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Formula milk versus term human milk for feeding preterm or low birth weight infants (Review)

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TABLE OF CONTENTS

[Intervention Review]

Formula milk versus term human milk for feeding preterm or low birth weight infants

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ABSTRACT

Background

Term (mature) human breast milk, compared with artificial formula milks, may provide insufficient nutrition for growth and development in preterm or low birth weight infants. However, human milk may confer advantages to infants in terms of a decreased incidence of adverse outcomes.

Objectives

To determine if formula milk compared with term human breast milk leads to improved growth and development without significant adverse effects in low birth weight or preterm infants.

Search methods

The standard search strategy of the Cochrane Neonatal Review Group was used. This included electronic searches of the Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library, Issue 4, 2003), MEDLINE 1966 - October 2003, EMBASE 1980 - October 2003, CINAHL 1982 - October 2003 and previous reviews including cross references.

Selection criteria

Randomised controlled trials comparing feeding with formula milk versus term human milk in low birth weight or preterm infants.

Data collection and analysis

Data were extracted using the standard methods of the Cochrane Neonatal Review Group, with separate evaluation of trial quality and data extraction by each author and synthesis of data using relative risk, risk difference and weighted mean difference.

Main results

Six trials, all initiated more than 20 years ago, fulfilled the pre-specified inclusion criteria. Four small trials compared feeding with standard calorie formula milk versus unfortified term human milk. Two trials compared feeding with calorie-enriched formula milk versus unfortified term human milk. No trials comparing feeding with formula milk versus nutrient-fortified term human milk were found. Only one trial reported longer term follow up of growth and development.

In preterm and low birth weight infants, enteral feeding with formula milk compared with unfortified term human milk resulted in a greater rate of growth in the short term. We did not find a statistically significant difference in the incidence of necrotising enterocolitis, but this

was evaluated as a pre-defined outcome in only one trial. The single trial that evaluated longer-term outcomes did not find evidence of an effect on longer-term growth and neurodevelopment.

Authors' conclusions

In preterm and low birth weight infants, feeding with formula milk, compared with unfortified term human milk, leads to a greater rate of growth in the short term. The limited data available do not allow definite conclusions on whether adverse outcomes, including necrotising enterocolitis, are increased in infants who receive formula milk compared with term human milk. There are no data from randomised trials on the comparison of feeding with formula milk versus nutrient-fortified breast milk. This limits the implications for practice of this review as nutrient fortification of breast milk is now a common practice in neonatal care. Future trials may compare growth, development and adverse outcomes in infants who receive adapted "preterm" formula milks versus nutrient-fortified human breast milk.

PLAIN LANGUAGE SUMMARY

Formula milk compared with breast milk for promoting growth in preterm or low birth weight infants

Breast milk may provide protective factors for a newborn baby's immune system. This milk may not, however, provide enough nutrition for babies born early or with a low birth weight. Artificial formula milks may better suit the specific nutritional needs of these infants. This review compared feeding preterm or low birth weight infants with formula milk versus term breast milk (the milk of mothers who have delivered a term infant) in six studies involving 481 infants. The results showed a greater rate of growth in the short term when fed formula milk instead of unfortified breast milk but no evidence of effect on long-term growth or development. Differences in feeding intolerance, diarrhoea, diseases of the small intestine and colon, vitamin D deficiency or fractures were not significant, partly due to small numbers of infants in the studies. Studies were undertaken in resource-rich countries only. They were initiated 20 years ago so that management of preterm and low birth weight babies and the content of formula has changed considerably since then.

BACKGROUND

Human breast milk, as the sole enteral feed for preterm or low birth weight infants, has putative advantages with regard to delivering immuno-protective factors such as secretory immunoglobulin-A, lysozyme and lactoferrin and in improving the mother-infant interaction (American Academy of Pediatrics and Workgroup on Breastfeeding 1997). Case-control data suggest a decreased incidence of adverse outcomes such as feed intolerance or significant gastrointestinal disease in infants nourished with human breast milk compared with formula milk (Beeby 1992). However, the nutritional requirements - calories, protein and minerals - of these infants, who are born with relatively impoverished nutrient reserves and are subject to additional metabolic stresses compared with term infants, may not be fully met by enteral feeding with human milk (Hay 1994; Schanler 1995). These deficiencies may have adverse consequences with regard to growth and bone mineralisation. Early postnatal nutrition during a very vulnerable period of brain growth may also affect later neurodevelopment (Lucas 1994). The role of nutrient fortification of human milk in influencing these outcomes in preterm or low birth weight infants is the subject of other Cochrane reviews (Kuschel 2000 a; Kuschel 2000 b; Kuschel 2000 c; Kuschel 2000 d).

Expressed breast milk for feeding preterm or low birth weight infants is not always or consistently available. Additionally, the delivered quality of expressed breast milk may be compromised by the prior method of milk storage and handling and the risk of microbial contamination. Because of these factors, plus concern regarding the nutritional adequacy of unfortified breast milk, a variety of artificial whole milk feeds have been assessed as alternative nutritional sources for preterm or low birth weight infants. An international consensus statement, based on data from growth and nutrient balance studies, has recommended energy, protein and mineral intakes to support intra-uterine accretion rates for formula fed stable/growing preterm infants (Tsang 1993). Energy requirements are approximately 120 kcal/kg/day with a corresponding protein input of 3 - 3.8 g/kg/day to provide the optimal protein:energy ratio. If feeding at 180 ml/kg/day, a formula milk will require an energy content of at least 68 kcal/100ml and a corresponding protein concentration of 1.7- 2.1 g/100ml. The recommended intakes of calcium (80- 120 mg/kg/d) and phosphorus (60- 140 mg/kg/day) are required to support intra-uterine accretion rates and to avoid metabolic bone disease due to mineral deficiency. The bioavailability of calcium from formula milk is approximately 60% and of phosphorus approximately 80% of intake (Schanler 1994). Therefore, a formula milk should contain calcium and phosphorus at a minimum approximate level of 75 mg/100ml and 42 mg/100ml respectively (if feeding at 180 ml/kg/day).

Artificial formula milks, mainly modified cow's milk, vary with regard to calorie, protein and mineral content but, broadly, can be considered as:
1. "Term" formulae; designed for term infants, based on the composition of mature breast milk. The typical energy content is 68 kcal/100ml. The concentration of protein is approximately 1.5 g/100ml and the calcium and phosphorus content 50 mg/100ml and 30 mg/100ml respectively (Fewtrell 1999). Some "term" formulae are further modified with regard to protein or mineral content.
2. "Preterm" formulae; designed for preterm infants. These are calorie-enriched (approximately 80 kcal/100ml) and variably protein- and mineral-enriched. The calorie content may be provided as protein, fat or carbohydrate and the balance between calories and protein may be critical in determining the type of growth. However, recent nutrient balance data have not supported the proposal that a formula with a higher protein:energy ratio would promote accretion rates of fat, fat-free mass, and minerals closer to those of the fetus (Fairey 1997).

The nutrient and non-nutrient content of breast milk is not constant. Human breast milk for feeding preterm or low birth weight infants may be either the expressed breast milk of the infant's mother or banked milk from donor mothers (and these may be mothers who have delivered preterm or term infants). The breast milk of mothers who deliver before term, typically the preterm baby's own mother's milk, has a higher protein, including host defence protein, content than term human milk (Gross 1980; Gross 1981). These differences may affect the relative suitability of term and preterm milks for feeding preterm and low birth weight infants (Gross 1983). Term human milk varies with regard to fat, energy and protein content depending upon the stage of lactation at which it is collected. Milk expressed from the donor's lactating breast has a higher calorie and protein content than that collected from the contralateral breast ("drip" breast milk) (Lucas 1978). This review will focus only on the comparison of formula milk with term human milk. The comparison of formula milk with preterm human milk is addressed in a separate review (McGuire 2001).

OBJECTIVES

To determine if formula milk compared with term (mature) human milk leads to improved growth and developmental outcomes without significant adverse effects in low birth weight (less than 2.5 kg) or preterm (less than 37 weeks gestation) infants.

In planned subgroup analyses, to determine the effects of feeding preterm or low birth weight infants with formula milk compared with term (mature) human milk, for the following types of formula milk:

1. "Term" formula milk: Standard-calorie (approximately 68 kcal/100ml), with protein concentration of less than 1.7 g/100ml.
2. "Term" formula milk: Standard-calorie (approximately 68 kcal/100ml), with protein enrichment to at least 1.7 g/100ml.
3. "Term" formula milk: Standard-calorie (approximately 68 kcal/100ml), enriched with protein (at least 1.7 g/100ml) and with calcium and phosphorus enrichment of at least 75 mg/100ml and at least 42 mg/100ml respectively.
4. "Preterm" formula milk: Calorie-supplemented (approximately 80 kcal/100ml or greater), with protein concentration of less than 1.7 g/100ml.
5. "Preterm" formula milk: Calorie-supplemented (approximately 80 kcal/100ml or greater), with protein enrichment to at least 1.7 g/100ml.
6. "Preterm" formula milk: Calorie-supplemented (approximately 80 kcal/100ml or greater), enriched with protein (at least 1.7 g/100ml) and with calcium and phosphorus enrichment of at least 75 mg/100ml and at least 42 mg/100ml respectively.

METHODS

Criteria for considering studies for this review

Types of studies

Controlled trials utilizing either random or quasi-random patient allocation.

Types of participants

Enterally fed preterm (less than 37 weeks gestation) or low birth weight infants (less than 2.5 kg), cared for in a hospital setting.

Types of interventions

Randomised and quasi-randomised controlled trials comparing feeding with formula milk versus term human milk. The allocated milk feed should form the entire enteral intake, not a supplement to the expressed breast milk of the mother. Trials in which parenteral nutritional support is available during the period of advancement of enteral feeds are acceptable, provided that the groups receive similar treatment other than the type of milk feed.

Types of outcome measures

1. Primary outcomes
a. Short term (prior to discharge from hospital) growth parameters: Time to regain birth weight, weight gain, linear growth, head growth, skinfold thickness
b. Longer term (following discharge from hospital) growth parameters: Weight gain, linear growth, head growth, skinfold thickness
c. Neurodevelopmental outcomes: Neurodevelopmental score during infancy and beyond using validated assessment tools

2. Secondary outcomes: Adverse events
a. Gastrointestinal disturbance such as feeding intolerance and diarrhoea
b. Necrotising enterocolitis
c. Fractures or clinical evidence of rickets

Search methods for identification of studies

See: Collaborative Review Group search strategy

We used the standard search strategy of the Cochrane Neonatal Review Group. This included electronic searches of the Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library, Issue 4, 2003), MEDLINE (1966 - October 2003), EMBASE (1980 - October 2003) and CINAHL (1982 to October 2003) (all accessed via OVID). We did not apply a language restriction. We examined references in studies identified as potentially relevant, and in previous reviews and standard textbooks of neonatal medicine and nutrition.

The search strategy involved the following combination of text words, subject headings and publication type: 1. "Infant-Newborn"/ all subheadings, 2. infan$, 3. neonat$, 4. prem$, 5. explode Infant, Premature/ or preemie, 6. low birth weight or explode Infant, Low Birth Weight/, 7. explode Infant, Low Birth Weight/ or LBW, 8. small for gest$, 9. light for gest$, 10. explode Fetal Growth Retardation/ or growth retard$, 11. IUGR, 12. growth restrict$, 13. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12, 14. explode Breast Feeding/ or explode Infant Nutrition/ or explode Feeding Methods/ or explode Bottle Feeding, 15. milk or explode Milk Banks/ or explode Milk, Human/ or explode Milk/, 16. explode Infant Food/ or formula milk, 17. 14 or 15 or 16, 18. 13 and 17, 19. Clinical Trial/, 20. 18 and 19.

Data collection and analysis

1. The studies identified by the above search strategy were screened (title and abstract) by two reviewers (GH and WM). The full text of the report of each study identified as of potential relevance was re-screened (full-text) by two reviewers (WM, MYA). These independent assessments followed pre-specified guidelines for inclusion. The decision to include or exclude a specific study was made by consensus of the reviewers.

2. We used the criteria and standard methods of the Cochrane Neonatal Review Group to assess the methodological quality of the included trials. We evaluated the quality of the trials in terms of allocation concealment, blinding of parents or carers and assessors to intervention, and completeness of assessment in all randomised individuals. Additional information was requested from the authors of each trial to clarify methodology and results as necessary.

3. We used a data collection form to aid extraction of relevant information and data from each included study. Each reviewer extracted the data separately, compared data, and resolved differences by consensus.

4. We used the standard methods of the Cochrane Neonatal Review Group to synthesize the data. Effects were expressed as relative risk (RR) and 95% CI and risk difference (RD) and 95% CI for categorical data, and mean difference (MD) and 95% CI for continuous data. A fixed effect model was planned for meta-analysis.

RESULTS

Description of studies

Eleven trials that appeared to be relevant were identified in the first round of screening. Six of these trials were included and these are detailed in the table, Characteristics of Included Studies. These studies varied with regard to entry criteria and outcome measures.

Raiha 1976 randomised 106 preterm infants, of birth weight less than 2.1 kg, within three gestational age categories (28 - 30 weeks, 31 - 33 weeks and 34- 36 weeks) to receive one of the following three types of milk:
1. Standard-calorie formula milk (with protein at 1.5 g/100ml): 43 infants randomised
2. Standard-calorie and protein-enriched formula milk (with protein at 3.0 g/100ml): 41 infants randomised
3. Pooled donor term human milk (unfortified): 22 infants randomised
In all of the formulae, calcium and phosphorus mean concentrations were 60 mg/100ml and 41.9 mg/100ml respectively. Infants with growth restriction or "physical abnormality or obvious disease" were excluded. Feeds were allocated within the first 24 hours of life and continued until a weight of 2.4 kg was attained or until infants were withdrawn from the study because of a "medical complication". Human milk fed infants were also given supplemental vitamins. Banked term human milk was given at a 170 ml/kg/day, compared with formulae at 150 ml/kg/day, in order to achieve equivalent calorie inputs. The primary goal of the study was to determine if the quantity and quality of protein intake affected short term growth and metabolic outcomes.

Subsequent publications from Raiha and colleagues reported largely on biochemical outcomes of infants in the same cohorts (Raiha 1976).

Davies 1977: 68 preterm infants were stratified by gestational age (28- 32 weeks and 33- 36 weeks) and randomised to feeding with a standard calorie, protein-enriched (2.7 g/100ml) and mineral-supplemented (calcium and phosphorus concentration 94 mg/100ml and 75 mg/100ml respectively) formula milk (34 infants) or unfortified term donor breast milk (34 infants). Feeds were assigned for the 2 month follow-up period. Mean weekly rates of change in weight, crown-heel length and head circumference from birth to one month and from one month to two months were reported.

Schultz 1980 randomly assigned 20 preterm and low birth weight infants to either a standard calorie protein-enriched (2.6 g/100ml) formula milk (10 infants) or to unfortified term donor breast milk (10 infants) for at least four weeks from birth. Time to regain birth weight and weekly rate of weight gain from birth, but no standard deviations or values to allow calculation of standard deviations, were published.

Gross 1983 randomised 47 infants, of gestational age 27- 33 weeks and birth weight less than 1600 g, to feeding with a standard-calorie (67 kcal/100ml), protein-enriched (1.9 g/100ml) formula milk with calcium and phosphorus concentrations of approximately 81 mg/100ml and 40 mg/100ml respectively (26 infants), or to unfortified term donor breast milk (21 infants). The feeds were assigned until the infant reached a weight of 1800g or until withdrawn from the study because of feed intolerance or necrotizing enterocolitis. Time to regain birth weight and mean daily rates of change in weight, crown-heel length and head circumference, from the point of regained birth weight until reaching a weight of 1800 g, were reported. Although the report gave information on adverse outcomes, the seven affected infants were withdrawn from the study and not included in the analyses of growth rates. Therefore, growth data are reported for 20 infants in each arm of the trial.

Tyson 1983 assigned randomly a total of 81 very low birth weight infants to feeding with either a "preterm" formula milk (44 infants) or pooled banked term human milk (37 infants). The formula milk was enriched with calories (87 kcal/100ml), and with protein (2.2 g/100ml). Calcium and phosphorus content was approximately 78 mg/100ml and 45 mg/100ml respectively, and so the formula meets our pre-specified criteria for mineral-enrichment. The feeds were not allocated until the tenth day of life in order to avoid the use of protein-enriched formula "when active growth was unlikely". In the first nine days of life the infants received a standard-calorie formula milk or maternal expressed breast milk. The feeds were assigned until the infant reached a weight of 2000 g or until withdrawn from the study because of "any illness requiring intravenous infusion of fat or protein". Mean daily rates of change in weight, crown-heel length and head circumference from the tenth until the thirtieth day of life were reported. Although the report gave information on adverse outcomes, including necrotising enterocolitis, the five affected infants were withdrawn from the study and not included in the analyses of growth rates. Therefore, growth data are reported for the remaining 76 infants in the trial.

Lucas 1984: Lucas and colleagues enrolled a total of 159 preterm infants, of birth weight less than 1850 g, in a randomised comparison of feeding with a "preterm" formula milk (76 infants) versus banked term human milk (83 infants) as the sole diet. A parallel study examined outcomes in infants fed formula milk or breast milk as a supplement to feeding with the breast milk of the infant's own mother: these data are not included in this review. The formula milk was enriched with calories (80 kcal/100ml), and with protein (2.0 g/100ml). Calcium and phosphorus content was approximately 75 mg/100ml and 35 mg/100ml respectively, and so the formula does not meet our pre-specified criteria for mineral-enrichment. The formula was intended to be delivered at 180 ml/kg/day versus the breast milk at 200 ml/kg/day. Feeds were assigned until the infant reached a weight of 2000 g or until discharge from the neonatal unit. The first "interim" report provided data on short term growth outcomes in a pre-defined subset of the total cohort recruited. Time to regain birth weight (62 infants) and rates of change in weight (58 infants), crown-heel length (26 infants) and head circumference (48 infants), from the point of regained birth weight until discharge from the neonatal unit or reaching a weight of 2000 g, were reported. Data on the incidence of necrotising enterocolitis were reported for all of the 159 infants recruited to the trial.

Lucas 1984 reported longer term follow-up data on the great majority of surviving infants in the trial. A validated neurological assessment (Ameil-Tison 1986) of 122 (85%) of the surviving infants at 9 and 18 months post term was reported. In the 110 surviving infants with no neurological impairment at 9 months post term, adaptive, gross motor, fine motor, language and personal-social skills were assessed using a developmental screening inventory devised by Knobloch 1966. For each field, a score adjusted for prematurity was calculated. An overall developmental quotient was calculated as the mean of the five scores attained by each infant.

Developmental assessments (Bayley Psychomotor and Mental Development Indices) at 18 months post term were reported for 114 of the 159 children originally enrolled in the study. 16 children had died and seven had been lost to follow-up. 12 children had cerebral palsy affecting fine motor skills, and these children were not assessed using the Bayley Psychomotor and Mental Development Indices. A further 10 infants were not assessed due to severe visual or hearing impairment or because follow up data were obtained by telephone for geographical reasons. Lucas 1984 did not report any statistically significant differences in the distribution of children not available for follow-up.

Longer term growth data were also reported. Trained assessors obtained anthropometric measurements, according to a standard protocol, in surviving children at 9 months (110 infants), 18 months (136 children) and 7.5- 8 years (130 children) post term.

Five studies were excluded and these are detailed in the table, Characteristics of Excluded Studies.

Armand 1996 reported a comparison of feeding with formula milk or with human milk in preterm infants. Although not clearly stated in the title or abstract, this was a non-randomised study.

Carey 1987 reported a comparison of formula feeds with human milk. Although not clearly stated in the title or abstract, this was a non-randomised study.

Narayanan 1982 reported a block randomised trial in low birth weight infants of feeding with formula milk versus "expressed human milk". Although not clear from the title and abstract, the "expressed human milk" group was allocated to enteral feeding with a mixture of preterm and term human milk (and these could not be separated into sub-groups).

Putet 1984 assigned 12 very low birth weight infants to feeding with a "preterm" formula milk or pooled term expressed breast milk, after full enteral feeding with breast milk had been established in both groups. Although not clear from the abstract, allocation does not appear to be random. There are statistically significant differences in the baseline characteristics of the two groups. The study authors have been contacted to provide further details of the allocation procedure.

In Svenningsen 1982, although the groups were said to have been randomly allocated, 12 of 18 in the human milk group were fed the preterm milk from their mother and 6 of 18 fed pooled fresh frozen donated breast milk (presumed mature, but not explicitly stated). The paper does not supply details allowing these sub-groups to be separated and so the data from this study were not included in the analysis. The author will be contacted to determine if this information is available.

Risk of bias in included studies

Quality assessments are included in the table, Characteristics of Included Studies.

Raiha 1976: Allocation to the formula milks was undertaken using a random sequence of four numbers, but every fifth infant was allocated to receive term human milk, so allocation concealment may have been sub-optimal. No attempt was made to blind parents, carers or assessors as to whether the infant received formula milk or human milk. The report gives outcome data on all randomised subjects, but it is unclear if the growth data refer also to infants recruited but subsequently excluded because of "a medical complication".

Davies 1977: There are no details on the method of randomisation or allocation concealment. No attempt was made to blind parents, carers or assessors to the type of milk given to the infant. The report gives outcome data on all randomised subjects.

Schultz 1980: There are no details on the method of randomisation or allocation concealment. No attempt was made to blind parents, carers or assessors to the type of milk given to the infant. The report gives outcome data on all randomised subjects.

Gross 1983: A random number table was utilised for randomisation. The study did not attempt blinding of parents, carers or assessors. Adverse events were not reported as a primary end-point but rather as withdrawal criteria. Therefore growth data do not refer to infants recruited but subsequently excluded because of feed intolerance or necrotising enterocolitis.

Tyson 1983: Sealed envelopes were used for randomisation. The study did not attempt blinding of parents, carers or assessors. Adverse events were not reported as a primary end-point but rather as withdrawal criteria. Therefore growth data do not refer to infants recruited but subsequently excluded because of adverse events, including necrotising enterocolitis, or because of lack of availability of human milk, or maternal concern regarding growth.

Lucas 1984 employed a randomisation sequence in sealed numbered envelopes. The study did not attempt blinding of parents, or carers or assessors prior to hospital discharge. Short term (prior to hospital discharge) growth data were published as an "interim" report on a pre-defined sub-group of the total trial cohort. Data on necrotising enterocolitis all of the 159 recruited infants were reported.

For Lucas 1984, the assessment of longer-term outcomes in infants was undertaken blind to the dietary intervention. Follow-up at 18 months was achieved for 96% of surviving infants who had received formula milk, and for 95% of surviving infants who had received breast milk. Growth performance in surviving children at 9 months were presented for 72% of surviving infants who had received formula milk, and for 82% of surviving infants who had received breast milk, and at 18 months post term for 96% of surviving infants who had received formula milk, and for 95% of surviving infants who had received breast milk. 84% of surviving infants who had received formula milk, and 87% of surviving infants who had received breast milk, were assessed neurodevelopmentally at 9 months and 18 months post term. At 7.5- 8 years post term, precise data on the number of surviving infants who were available for follow-up in each feeding group are not published, but it is likely that greater then 90% of surviving infants who had received either breast milk or formula as a sole diet were assessed.

Effects of interventions

1. Primary outcomes:

Short term growth parameters:

Time to regain birth weight was reported in four of the included studies:

Raiha 1976 reported mean time to regain birth weight as statistically significantly lower in the formula fed group (13.5 versus 16.3 days).

Gross 1983 reported mean time to regain birth weight as statistically significantly lower in the formula fed group, excluding those randomised but subsequently withdrawn because of feed intolerance or necrotising enterocolitis (10.3 versus 18.8 days).

The data from these two reports were combined. The formula fed group, compared to those allocated to feeding with term human milk, regained birth weight more quickly: Weighted mean difference: -5.0 days (95% confidence interval -7.2, -2.7).

Schultz 1980 reported the mean time to regain birth weight as 2.5 weeks in the formula fed group, compared with 1.5 weeks in the human milk fed group. This was stated to be a non-significant difference. However, no standard deviation, or statistic to allow calculation of standard deviation, was reported and the data could not be included in a meta-analysis. The author will be contacted to ask if such data are available.

Lucas 1984 reported the median time to regain birth weight as statistically significantly lower in the formula fed infants (10 days versus 16 days). However, no standard deviation, or statistic to allow calculation of standard deviation, was reported and the data could not be included in a meta-analysis. The author will be contacted to ask if such data are available.

Sub-group analysis of time to regain birth weight:

1. "Term" formula milk: Standard-calorie with protein concentration of less than 1.7 g/100ml. Raiha 1976 reported the mean time to regain birth weight as lower in the formula fed group compared with the human milk fed group (13.3 versus 16.3 days). The difference was not statistically significant: Mean difference (MD) -6.0 days (95% confidence interval -6.2, 0.1).

2. "Term" formula milk: Standard-calorie with protein enrichment to at least 1.7 g/100ml. Raiha 1976 reported the mean time to regain birth weight as lower in the formula fed group (13.7 versus 16.3 days). Gross 1983 reported the mean time to regain birth weight as statistically significantly lower in the formula fed infants, excluding those randomised but withdrawn because of feed intolerance or necrotising enterocolitis (10.3 versus 18.8 days). The data from these two reports were combined. The formula fed group regained birth weight more quickly: Weighted mean difference: -5.0 days (95% confidence interval -7.3, -2.6).

Short term change in weight:

Raiha 1976 reported a statistically significantly greater rate of weight gain, from the point of regained birth weight until attaining a weight of 2400 g, in the formula fed infants.

Davies 1977 did not find any statistically significant difference in rate of weight gain, measured from birth to two months, in infants allocated to receive formula milk versus term human milk.

Gross 1983 reported a statistically significantly greater rate of weight gain, from the point of regained birth weight until attaining a weight of 1800 g, in the formula fed group of infants, excluding those randomised but withdrawn subsequently because of feed intolerance or necrotising enterocolitis.

Tyson 1983 reported a statistically significantly greater rate of weight gain, from the point of entry into the trial (day 10) until day 30, in the formula fed group of infants, excluding those randomised but withdrawn subsequently because of an adverse event.

The data from the above reports were combined. The formula fed group had a statistically significantly greater rate of weight gain in the short term: Weighted mean difference: 6.1 g/day (95% confidence interval 4.9, 7.3).

Schultz 1980 did not find any statistically significant difference in the rate of weight gain, from the point of regained birth weight. However, no standard deviation, or statistic to allow calculation of standard deviation, was reported. The data could not be included in this meta-analysis. The author will be contacted to obtain further data to allow calculation of a standard deviation.

Lucas 1984 reported a statistically significantly greater rate of weight gain, from the point of regained birth weight until discharge from the neonatal unit or reaching a weight of 2000 g, in the formula fed group of infants. Weighted mean difference: 5.2 g/kg/day (95% confidence interval 2.9, 7.5). As data were given as g/kg/day, as opposed to g/day (without data to allow conversion to g/day), these data could not be incorporated in a meta-analysis with the data from the studies by Raiha 1976, Davies 1977, and Gross 1983.

Subsequent reports from Lucas and colleagues provided details of short term growth in a larger cohort than the pre-defined sub-group presented in the first "interim" report (Lucas 1984). However, short term growth data were presented only for those infants who were available for assessment at 9 or 18 months or at 7.5 - 8 years. The data presented do not refer to all of the infants in whom short term growth was measured. Specifically, data were not presented for those infants who subsequently died or were lost to follow-up before assessment at 9 months, 18 months or 7.5 - 8 years. The author has been contacted to request access to the early growth outcomes for all of the infants randomised to the trial of feeding with preterm formula milk versus donor term human milk. In the meantime, the additional short term growth data reported have not been included in this review.

Sub-group analyses of short term change in weight:

1. "Term" formula milk: Standard-calorie with protein concentration of less than 1.7 g/100ml. Raiha 1976 reported a statistically significantly greater rate of weight gain, from the point of regained birth weight until attaining a weight of 2400 g, in the formula fed group of infants. Weighted mean difference: 2.3 g/day (95% confidence interval 0.4, 4.2).

2. "Term" formula milk: Standard-calorie with protein enrichment to at least 1.7 g/100 ml. Raiha 1976 did not find any statistically significant difference in the rate of weight gain, from the point of regained birth weight until attaining a weight of 2400 g, in the formula fed versus the human milk fed group of infants. Gross 1983 reported a statistically significantly greater rate of weight gain, from the point of regained birth weight until attaining a weight of 1800 g, in the formula fed group of infants, excluding those randomised but withdrawn subsequently because of feed intolerance or necrotising enterocolitis. The data from these reports were combined. The formula fed group had a statistically significantly greater rate of weight gain in the short term: Weighted mean difference: 5.4 g/day (95% confidence interval 4.0, 6.9).

3. "Term" formula milk: Standard-calorie, protein-enriched and calcium and phosphorus supplemented to at least 75 mg/100ml and 42 mg/100ml respectively. Davies 1977 did not find any statistically significant difference in the rate of weight gain, measured from birth to two months, in infants allocated to receive formula milk versus term human milk: Weighted mean difference: 4.2 g/day (95% confidence interval -0.5, 8.9).

4. "Preterm" formula milk: Calorie-supplemented, protein-enriched and calcium and phosphorus supplemented to at least 75 mg/100ml and 42 mg/100ml respectively. Tyson 1983 reported a statistically significantly greater rate of weight gain, measured from day 10 until day 30, in the formula fed group of infants, excluding those randomised but withdrawn subsequently because of an adverse event: Weighted mean difference: 14.5 g/day (95% confidence interval 10.9, 18.1).

Short term linear growth: Crown-heel length:

Davies 1977 did not find any statistically significant difference in the rate of increase in crown-heel length, measured from birth to two months, in infants allocated to receive formula milk versus term human milk.

Gross 1983 reported a statistically significantly greater rate of increase in crown-heel length, measured from birth, in the formula fed infants, excluding those randomised but

withdrawn subsequently because of feed intolerance or necrotising enterocolitis.

Tyson 1983 reported a statistically significantly greater rate of increase in crown-heel length, from the point of entry into the trial (day 10) until day 30, in the formula fed infants, excluding those randomised but withdrawn subsequently because of an adverse event.

Lucas 1984 reported a statistically significantly greater rate of increase in crown-heel length, measured from birth until discharge from the neonatal unit or reaching a weight of 2000 g, in the formula fed infants.

The data from these four reports were combined. The formula fed group demonstrated a statistically significantly greater rate of increase in crown-heel length in the short term: Weighted mean difference: 1.7 mm/week (95% confidence interval 1.1, 2.4).

Sub-group analyses of short term linear growth: Crown-heel length:

1. "Term" formula milk: Standard-calorie with protein enrichment to at least 1.7 g/100ml. Gross 1983 reported a statistically significantly greater rate of increase in crown-heel length, measured from birth, in the formula fed group of infants, excluding those randomised but withdrawn subsequently because of feed intolerance or necrotising enterocolitis: Weighted mean difference: 1.8 mm/week (95% confidence interval 0.7, 2.9).

2. "Term" formula milk: Standard-calorie, protein-enriched and calcium and phosphorus supplemented to at least 75 mg/100ml and 42 mg/100ml respectively. Davies 1977 did not find any statistically significant difference in the rate of increase in crown-heel length, measured from birth to two months, in infants allocated to receive formula milk versus term human milk: Weighted mean difference: 0.8 mm/week (95% confidence interval -0.2, 1.8).

3. "Preterm" formula milk: Calorie-supplemented, with protein enrichment to at least 1.7 g/100ml. Lucas 1984 reported a statistically significantly greater rate of increase in crown-heel length, measured from birth until discharge from the neonatal unit or reaching a weight of 2000 g, in the formula fed infants. Weighted mean difference: 2.4 mm/week (95% confidence interval 0.6, 2.2).

4. "Preterm" formula milk: Calorie-supplemented, protein-enriched and calcium and phosphorus supplemented to at least 75 mg/100ml and 42 mg/100ml respectively. Tyson 1983 reported a statistically significantly greater rate of increase in crown-heel length, from the point of entry into the trial (day 10) until day 30, in the formula fed group of infants, excluding those randomised but withdrawn subsequently because of an adverse event: Weighted mean difference: 4.0 mm/week (95% confidence interval 1.9, 6.1).

Short term linear growth: Crown-rump length:

Raiha 1976 reported a statistically significantly greater rate of increase in crown-rump length, measured from birth, in the formula fed infants: Weighted mean difference: 0.6 mm/week (95% confidence interval 0.1, 1.1).

Sub-group analyses of short term linear growth: Crown-rump length:

1. "Term" formula milk: Standard-calorie with protein concentration of less than 1.7 g/100ml. Raiha 1976 did not find any statistically significant difference in the rate of increase in crown-rump length, measured from birth, in infants allocated to receive formula milk versus term human milk: Weighted mean difference: 0.6 mm/week (95% confidence interval -0.3, 1.5).

2. "Term" formula milk: Standard-calorie with protein enrichment to at least 1.7 g/100ml. Raiha 1976 did not find any statistically significant difference in the rate of increase in crown-rump length, measured from birth, in infants allocated to receive formula milk versus term human milk: Weighted mean difference: 0.3 mm/week (95% confidence interval -0.3, 0.9).

Short term linear growth: Femoral length:

Raiha 1976 reported a statistically significantly greater rate of increase in femoral length, measured from birth, in the formula fed infants: Weighted mean difference: 0.4 mm/week (95% confidence interval 0.2, 0.6).

Sub-group analyses of short term linear growth: Femoral length:

1. "Term" formula milk: Standard-calorie with protein concentration of less than 1.7 g/100ml. Raiha 1976 reported a statistically significantly greater rate of increase in femoral length, measured from birth, in the formula fed infants: Weighted mean difference: 0.3 mm/week (95% confidence interval 0.1, 0.5).

2. "Term" formula milk: Standard-calorie with protein enrichment to at least 1.7 g/100ml. Raiha 1976 reported a statistically significantly greater rate of increase in femoral length, measured from birth, in the formula fed infants: Weighted mean difference: 0.5 mm/week (95% confidence interval 0.3, 0.7).

Short term head growth: Occipto-frontal head circumference:

Davies 1977 did not find any statistically significant difference in the rate of increase in occipto-frontal head circumference, measured from birth, in infants allocated to receive formula milk versus term human milk.

Gross 1983 reported a statistically significantly greater rate of increase in occipto-frontal head circumference, measured from birth, in the formula fed infants, excluding those randomised but withdrawn subsequently because of feed intolerance or necrotising enterocolitis.

Tyson 1983 found a statistically significantly greater rate of increase in occipto-frontal head circumference, measured from the point of entry into the trial (day 10) until day 30, in the formula fed group of infants, excluding those randomised but withdrawn subsequently because of an adverse event.

Lucas 1984 did not find any statistically significant difference in the rate of increase in occipto-frontal head circumference, measured from birth, in the formula fed versus the human milk fed infants.

The data from these four reports were combined. The formula fed group, compared to those allocated to feeding with term human milk, demonstrated a statistically significantly greater rate of increase in occipto-frontal head circumference: Weighted mean difference: 1.6 mm/week (95% confidence interval 1.0, 2.2).

Sub-group analyses of short term head growth: Occipto-frontal head circumference:

1. "Term" formula milk: Standard-calorie with protein enrichment to at least 1.7 g/100 ml. Gross 1983 reported a statistically significantly greater rate of increase in occipto-frontal head circumference, measured from birth, in the formula fed group of infants, excluding those randomised but withdrawn subsequently because of feed intolerance or necrotising enterocolitis: Weighted mean difference: 1.8 mm/week (95% confidence interval 0.8, 2.8).

2. "Term" formula milk: Standard-calorie, protein-enriched and calcium and phosphorus supplemented to at least 75 mg/100ml and 42 mg/100ml respectively. Davies 1977 did not find any statistically significant difference in the rate of increase in occipto-frontal head circumference, measured from birth to two months, in infants allocated to receive formula milk versus term human milk: Weighted mean difference: 0.6 mm/week (95% confidence interval -0.3, 1.5).

3. "Preterm" formula milk: Calorie-supplemented (approximately 80 kcal/100ml or greater), with protein enrichment to at least 1.7 g/100ml. Lucas 1984 did not find any statistically significant difference in the rate of increase in occipto-frontal head circumference, measured from birth until discharge from the neonatal unit or reaching a weight of 2000 g, in the formula fed compared with the human milk fed group of infants: Weighted mean difference: 2.4 mm/week (95% confidence interval -6.6, 11.6).

4. "Preterm" formula milk: Calorie-supplemented, protein-enriched and calcium and phosphorus supplemented to at least 75 mg/100ml and 42 mg/100ml respectively. Tyson 1983 reported a statistically significantly greater rate of increase in occipto-frontal head circumference, measured from the point of entry into the trial (day 10) until day 30, in the formula fed infants, excluding those randomised but withdrawn subsequently because of an adverse event: Weighted mean difference: 4.0 mm/week (95% confidence interval 2.5, 5.5).

Short term mean change in skinfold thickness:

Only the study by Tyson 1983 reported the short term mean change in (triceps) skinfold thickness. Tyson 1983 reported a statistically significant greater rate of increase in triceps skinfold thickness, measured from the point of entry into the trial (day 10) until day 30, in the formula fed group of infants, excluding those randomised but withdrawn subsequently because of an adverse event: Weighted mean difference: 0.04 mm/week (95% confidence interval 0.01, 0.27).

Longer term (following discharge from hospital) growth parameters:

Longer term growth data were reported on the cohort of infants recruited by Lucas 1984. Of the original cohort of 159 infants, 110 infants were assessed at 9 months, 136 at 18 months, and 130 at 7.5- 8 years post-term. None of the other included studies reported growth following hospital discharge.

Lucas 1984 did not find any statistically significant differences in the weight, length, head circumference, subscapular skinfold thickness, triceps skinfold thickness or body mass index at 9 months or 18 months or 7.5- 8 years post-term in the "preterm" formula milk fed compared with the human milk fed group of infants.

Neuro-developmental outcomes:

These are reported only by Tyson 1983 and Lucas 1984. Longer term neurodevelopmental outcomes were not reported by Gross 1983. However, a subsequent report, only in abstract form stated that, at 6 months and 15 months corrected age, the cohort (40 infants/children) were reviewed (Gross 1986). Although, no data were presented, both groups were reported to have "similar patterns of growth" and to exhibit "no difference" in Bayley Mental or Psychomotor Developmental Indices. Further details and data have been requested from the author of the report.

Tyson 1983 measured Brazelton Neonatal Behavioural Assessment Scales at 37 weeks post-menstrual age (Brazelton 1976). The group of infants who received term formula milk had statistically significantly greater mean scores for response to visual and auditory stimuli: Weighted mean difference: 0.8 (95% confidence interval 0.3, 1.3) and for response to inanimate objects: Weighted mean difference: 2.5 (95% confidence interval 1.4, 3.7).

Lucas 1984 assessed 122 of the 143 surviving infants at 9 months and at 18 months post term. At 9 months, four of 66 infants who were allocated to receive donor term human milk, and eight of 56 of those allocated to receive "preterm" formula milk, had evidence of neurological impairment (Ameil-Tison 1986). At 18 months, four of 66 versus seven of 56 of the respective groups had evidence of neurological impairment. Neither comparison demonstrated a statistically significant difference.

Lucas 1984 did not find any statistically significant differences in developmental quotient or in adaptive, gross motor, fine motor, language and personal-social skills (Knobloch 1966) in the group of infants allocated to receive calorie-enriched and protein-supplemented formula milk compared with term human milk.

Lucas 1984 did not find any statistically significant differences in Bayley Psychomotor and Mental Development Indices at 18 months post term in the group of infants allocated to receive calorie-enriched and protein-supplemented formula milk compared with term human milk. Bayley Mental Development Index: Weighted mean difference: 0.5 (95% confidence interval -6.2, 7.2). Bayley Psychomotor Index: Weighted mean difference: 1.2 (95% confidence interval -4.4, 6.8).

2. Secondary outcomes: Adverse events

Only three of the included studies reported adverse events. Gross 1983 reported the incidence of feed intolerance and necrotising enterocolitis as withdrawal criteria, rather than as outcome measures. The data presented allow for ascertainment of adverse outcomes from each of the originally randomised groups. Similarly, Tyson 1983 reported chronic diarrhoea and necrotising enterocolitis as withdrawal criteria, allowing the incidence of the adverse events in each of the randomised groups to be determined. Lucas 1984 reported on necrotising enterocolitis in all of the 159 infants recruited to the comparison of feeding with "preterm" formula milk versus term human milk.

a. Feed intolerance or diarrhoea:

Gross 1983 reported that six of 26 infants originally randomised to receive formula milk feeds, compared with one of 21 infants originally randomised to receive term human milk, developed feed intolerance. Tyson 1983 reported that two of 44 infants originally randomised to receive formula milk feeds, compared with one of 37 infants originally randomised to receive term human milk, developed feed intolerance or chronic diarrhoea. The data from the two studies were combined in a meta-analysis. The difference is not statistically significant: Relative risk: 3.3 (95% confidence interval 0.7, 14.8); risk difference: 0.08 (95% confidence interval -0.01, 0.16).

Sub-group analyses of feed intolerance or diarrhoea:
1. "Term" formula milk: Standard-calorie with protein enrichment to at least 1.7 g/100ml. Gross 1983 did not find any statistically significant difference in the incidence of feed intolerance in infants randomised to receive formula milk feeds, compared with infants randomised to receive term human milk: Relative risk: 4.9 (95% CI 0.6, 37.2); risk difference: 0.18 (95% confidence interval 0.00, 0.37).

2. "Preterm" formula milk: Calorie-supplemented, protein-enriched and calcium and phosphorus supplemented to at least 75 mg/100ml and 42 mg/100ml respectively. Tyson 1983 did not find any statistically significant difference in the incidence of feed intolerance or diarrhoea in infants randomised to receive formula milk feeds versus term human milk: Relative risk: 1.7 (95% CI 0.2, 17.8); risk difference: 0.02 (95% confidence interval -0.06, 0.1).

b. Necrotising enterocolitis:

Gross 1983 did not find any statistically significant difference in the incidence of necrotising enterocolitis in infants randomised to receive formula milk feeds compared with term human milk: Three of 26 infants originally randomised to receive formula milk feeds, compared with one of 21 infants randomised to receive human milk, developed necrotising enterocolitis. Tyson 1983 reported that two of 44 infants randomised to receive formula milk feeds, compared with one of 37 infants randomised to receive term human milk, developed confirmed or suspected necrotising enterocolitis; the difference is not statistically significant. Lucas 1984 did not find any statistically significant difference in the incidence of necrotising enterocolitis in infants randomised to receive formula milk feeds versus term human milk: Six of 76 infants randomised to receive formula milk feeds, compared with three of 83 infants randomised to receive human milk, developed necrotising enterocolitis. These data from the three trials were combined in a meta-analysis: Relative risk: 2.5 (95% confidence interval 0.9, 7.3); risk difference: 0.05 (95% confidence interval 0.00, 0.1). We therefore do not find any statistically significant difference in the risk of necrotising enterocolitis with formula milk versus term human milk feeding.

Sub-group analyses of necrotising enterocolitis:

1. "Term" formula milk: Standard-calorie with protein enrichment to at least 1.7 g/100ml. Gross 1983 did not find any statistically significant difference in the incidence of necrotising enterocolitis in infants randomised to receive formula milk feeds versus term human milk: Relative risk: 2.4 (95% confidence interval 0.3, 21.6); risk difference: 0.07 (95% confidence interval -0.09, 0.22).

2. "Preterm" formula milk: Calorie-supplemented (approximately 80 kcal/100ml or greater), with protein enrichment to at least 1.7 g/100ml. Lucas 1984 did not find any statistically significant difference in the incidence of necrotising enterocolitis in infants randomised to receive formula milk feeds versus term human milk: Relative risk: 2.2 (95% confidence interval 0.6, 8.4); risk difference: 0.04 (95% confidence interval -0.03, 0.12).

3. "Preterm" formula milk: Calorie-supplemented, protein-enriched and calcium and phosphorus supplemented to at least 75 mg/100ml and 42 mg/100ml respectively. Tyson 1983 did not find any statistically significant difference in the incidence of necrotising enterocolitis in infants randomised to receive formula milk feeds versus infants randomised to receive preterm human milk: Relative risk: 4.2 (95% CI 0.2, 85.3); risk difference: 0.05 (95% confidence interval -0.03, 0.12).

c. Fractures or clinical evidence of rickets:

There are no data on fractures or clinical evidence of rickets presented in any of the included studies.

DISCUSSION

The data available from the included trials support the view that, compared with infants who receive unfortified term human milk, preterm or low birth weight infants who receive standard-calorie "term" formula milk or calorie-enriched "preterm" formula milk regain birth weight more quickly and have a greater rate of short term growth. However, it should be noted that two trials (Gross 1983 and Tyson 1983) used feed intolerance and/or necrotising enterocolitis as withdrawal criteria and excluded infants who developed those complications after randomisation from analysis of short term growth rates. Because such infants may have been more fragile at trial entry and because those complications tended to be more frequent in the formula milk groups, these exclusions may have somewhat exaggerated the reported increase in short term growth among infants randomised to formula milk.

Four of the included studies examined outcomes in infants who received standard-calorie "term" formula milk (Raiha 1976; Davies 1977; Schultz 1980; Gross 1983). Although the number of infants in the trials was small, sub-group analyses of feeding with protein-enriched and with protein- and mineral-enriched standard-calorie formula milk versus term human milk were possible. In each sub-group, feeding with formula milk was associated with a greater rate of increase in at least one of the measured growth parameters. It should also be noted that the growth rate data published by Gross 1983 and Raiha 1976, but not by Davies 1977, excluded the initial growth phase until birth weight was regained. By definition, this phase will have been a period of weight loss. Therefore the reported rate of weight gain will be an over-estimate of the true overall rate from birth. This may serve to exaggerate the weighted mean difference when the data are combined with the growth data reported by Davies 1977. Unfortunately, the data reported by Schultz 1980, although suggesting an opposite trend in terms of days to regain birth weight and subsequent rate of weight gain, did not include a standard deviation with each mean value and could not be incorporated in a summary estimate. The relevant data have been requested. There are no longer term outcome data available from the trials that compared feeding with standard-calorie formula milk versus term human milk.

The two trials that compared feeding with "preterm" formula milk versus term human milk demonstrated greater rates of growth in the short term in the group that received formula milk (Tyson 1983; Lucas 1984). This is consistent with the greater calorie and

protein content of the nutrient-enriched formula compared with term human milk, especially the "drip" human milk used in the trial by Lucas 1984.

Lucas 1984 reported longer term follow up of growth and development of the recruited infants. Assessment at 9 months, 18 months, and 7.5- 8 years post term revealed no differences in longer term growth. Consequently, Lucas and colleagues have suggested that the preterm period is not a critical window for nutritional programming of growth. Similarly, Lucas 1984 found no evidence of an effect on later neurodevelopmental outcomes. The authors have suggested that feeding with human milk may still confer benefits for neurodevelopment, but that in this trial these have been offset by the potentially deleterious effects of the low nutrient content of "drip" human breast milk. The same workers have reported a non-randomised comparison of feeding preterm infants with the infant's own maternal breast milk (as maternal choice) versus formula milk. Neurodevelopmental scores and intelligence quotient were greater in the human milk fed infants (Morley 1988, Lucas 1992). However, the authors point out that the preterm infants who received maternal breast milk may have been subject to many known and unknown confounding factors that act as determinants of later development and intelligence.

We found no evidence that enteral feeding with formula milk versus term human milk was associated with an increased rate of feed intolerance. However, these data came from two small studies (Gross 1983; Tyson 1983) and the 95% confidence intervals of the risk estimates were wide. Since no attempts were made to blind parents, carers or assessors, the possibility that these are biased outcomes remains.

Does formula milk increase the risk of necrotising enterocolitis, or breast milk protect against necrotising enterocolitis, in preterm or low birth weight infants? This remains a question of major clinical importance in neonatal medicine. We have found no evidence that formula milk feeding increased the incidence of necrotising enterocolitis in preterm or low birth weight infants. However, this outcome was reported in only three of the included studies, with a total sample size of 287 infants (Gross 1983; Tyson 1983; Lucas 1984). In two of the studies, necrotising enterocolitis was reported as a withdrawal criterion rather than an outcome measure (Gross 1983, Tyson 1983). In the trial by Lucas 1990, infants were allocated to receive formula milk at 180 ml/kg/day versus breast milk at 200 ml/kg/day. This difference in delivered volume of enteral feed may have affected the risk of development of necrotising enterocolitis. Additional caution should be exercised in applying these data as growth-restricted preterm infants (or sick infants) were excluded from the study by Gross 1983. This sub-population may be at increased risk of developing necrotising enterocolitis (McDonnell 1994). An associated Cochrane review found no evidence that feeding with formula milk versus preterm human milk affected the incidence of necrotising enterocolitis in preterm or low birth weight infants (McGuire 2001). The data from the two reviews may be combined to help further address this question.

We found no data from randomised trials which compared formula milk with nutrient-fortified human milk. This limits the implications for practice of this review as nutrient fortification of human milk is now a common practice in neonatal care (Kuschel 2000 a; Kuschel 2000 b; Kuschel 2000 c; Kuschel 2000 d).

Other factors that limit the applicability of the findings of this review to current practice are:

1. The limited data from the studies by Gross 1983; Tyson 1983 and Lucas 1984 do not allow definite conclusions on whether adverse outcomes, including necrotising enterocolitis, are increased in infants who receive formula milk compared with term human milk.
2. The data in this review are from trials undertaken in resource-rich countries. In resource-poor countries, where the risk of infection in the neonatal period may be greater, the putative anti-infective properties of breast milk may confer advantages that outweigh the lower rate of short term growth. In India, a randomised trial in low birth weight infants "at risk of infection" found that serious infections (diarrhoea, pneumonia, septicaemia) were statistically significantly less common in infants allocated to received "expressed human milk" versus formula milk (Narayanan 1982). "Expressed human milk" in this study referred to a mixture of preterm and term human milk. As these could not be separated into sub-groups, the data could not be included in this review, but may be suitable for inclusion in a systematic review of randomised controlled trials of feeding with formula milk versus (term and preterm) human milk.
3. The included studies were initiated over 20 years ago. Since then, in addition to changes in the availability of formula milks and fortifiers for human milk, there have been changes to other aspects of the antenatal and subsequent management of preterm and low birth weight infants. It may be that the findings of this review are not wholly applicable to the modern population of even more preterm and even lower birth weight infants.

AUTHORS' CONCLUSIONS

Implications for practice

Feeding with formula milk, compared with term human milk, leads to improved short term growth in preterm or low birth weight infants, but there is no evidence of an effect on longer term growth or development. However, there are no data from randomised trials on the comparison of feeding with formula milk versus nutrient-fortified human milk. This limits the implications for practice of this review as nutrient fortification of human milk is now a common practice in neonatal care (Kuschel 2000a; Kuschel 2000b; Kuschel 2000c; Kuschel 2000d).

Implications for research

These relate mainly to the putative contribution of breast milk to protection against necrotising enterocolitis. In situations where the expressed breast milk of the infant's mother is not consistently available, could the risk of developing necrotising enterocolitis be reduced by the inclusion of donor breast milk as a component of the enteral intake of preterm or low birth weight infants? Further studies should compare enteral feeding with nutrient-enriched "preterm" formula milk versus nutrient-fortified term human milk in a population of infants at increased risk of necrotising enterocolitis, such as very low birth weight infants (birth weight less than 1500 g). Such an intervention would rely on the re-establishment and use of donor milk banks with the ability to screen for transmissible infectious agents. In situations where no breast milk is available, could supplementation of formula milk with a breast milk factor, such as immunoglobulin, reduce the incidence of NEC? Another Cochrane review has suggested the need for further trials in this area (Foster 2001). Future trials should attempt to ensure that carers and assessors are blind

to the intervention. Although more easily achievable for the longer term assessments, this is also important with regard to ascertainment of adverse events, such as feed intolerance and necrotising enterocolitis, where the threshold for investigation or diagnosis may be affected by knowledge of the intervention. Such a trial would require recruitment of approximately 900 infants to detect the estimated size of effect on the incidence of necrotising enterocolitis found in this review (95% confidence and at 80% power).

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Morley 1988

Morley R, Cole TJ, Powell R, Lucas A. Mother's choice to provide breast milk and developmental outcome. *Arch Dis Child* 1988;**63**:1382-1385.

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Schanler RJ, Rifka M. Calcium, phosphorus and magnesium needs for low birth weight infants. *Acta Paediatr Scand* 1994;**405 (suppl)**:111-116.

Schanler 1995

Schanler RJ. Suitability of human milk for the low-birthweight infant. *Clin Perinatol* 1995;**22**:207-22.

Tsang 1993

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References to other published versions of this review

McGuire 2001a

McGuire W, Anthony MY. Formula milk versus term human milk for feeding preterm or low birth weight infants (Cochrane Review). *The Cochrane Library* 2001, Issue 4.

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Davies 1977

Methods	1. Blinding of randomisation: Can't tell 2. Blinding of intervention: No 3. Complete follow up: Yes 4. Blinding of outcome measurement: No
Participants	68 preterm infants: 28-36 weeks in two strata. Exclusions: multiple births, congenital abnormalities and chromosomal disorders, congenital infection. Growth restricted infants (<5th percentile) may also have been excluded. Department of Child Health, University Hospital of Wales, Cardiff. 1972- 73.
Interventions	Standard calorie, protein-enriched, mineral-supplemented formula milk (N= 34) versus pooled term donated breast milk (N= 34). Assigned from birth for 2 months.
Outcomes	Rates of weight gain, increase in head circumference and length from birth until 1 month and from 1 month until 2 months.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Gross 1983

Methods	1. Blinding of randomisation: Yes 2. Blinding of intervention: No 3. Complete follow up: No 4. Blinding of outcome measurement: Can't tell
Participants	47 preterm infants (27- 33 weeks). Birth weight <1600g. Excluded if "congenital anomaly or major disease". Dept of Pediatrics, Duke University, USA. 1980- 82.
Interventions	Standard calorie, pretein-enriched formula milk (N= 26) versus pooled, Pasteurised, term, donated, milk (N=21). Feeds were assigned until the infant reached a weight of 1800g or until withdrawn from the study because of feed intolerance or necrotising enterocolitis.
Outcomes	Time, from birth, to regain birth weight. Mean daily gain in weight, length and head circumference, from regaining birth weight until reaching 1800g. Data on adverse events can be determined although these were not primary end-points of the study.
Notes	Feed intolerance and necrotising enterocolitis reported as withdrawal criteria, rather than as outcomes.

Risk of bias

Bias	Authors' judgement	Support for judgement

Gross 1983 *(Continued)*

Allocation concealment (selection bias)	Low risk	A - Adequate

Lucas 1984

Methods	1. Blinding of randomisation: Yes 2. Blinding of intervention: No 3. Complete follow up: Yes 4. Blinding of outcome measurement: Can't tell
Participants	159 infants of birth weight <1850g. Stratified by birth weight <1200g and 1201- 1850g. Infants with congenital abnormalities excluded. Infants with intra-uterine growth restriction not excluded. Study undertaken in the early 1980's in neonatal units in Anglia region of the UK.
Interventions	Calorie and protein (but not mineral)-enriched formula milk (N= 76) versus term pooled donor (mainly drip) breast milk (N= 83).
Outcomes	Short term outcomes: Time, from birth, to regain birth weight. Rates of change in weight (58 infants), crown-heel length (26 infants) and head circumference (48 infants) from the point of regained birth weight until discharge from the neonatal unit or reaching a weight of 2000 g. Incidence of necrotising enterocolitis- suspected and confirmed reported on complete cohort of 159 infants. Longer term outcomes: Validated neurological assessment, at 9 and 18 months, in 122 (85%) of surviving infants. Developmental quotient, adaptive developmental score, gross motor developmental score, fine motor developmental score, language developmental score, personal-social developmental score at 9 months (in 110 surviving infants without neurological impairment) Bayley mental development index and psychomotor development index at 18 months, corrected for preterm gestation, in 114 (94%) of surviving infants suitable for the assessment. Growth performance in surviving infants (weight, length and head circumference) at 9 months (110 infants), 18 months (136 infants), and 7.5- 8 years (130 infants) post term.
Notes	"Interim" report on short term growth in a sub-group of the trial cohort.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Raiha 1976

Methods	1. Blinding of randomisation: Yes (only for formula milk groups) 2. Blinding of intervention: No 3. Complete follow up: Yes 4. Blinding of outcome measurement: Can't tell
Participants	Infants of gestational age 28- 36 weeks and birth weight less than 2100g, but between 10th and 90th centiles for birth weight. Infants excluded if evidence of "physical abnormality or obvious disease". Study undertaken in the Premature Unit, Helsinki University Children's Hospital between 1972 and 1975.

Raiha 1976 *(Continued)*

Interventions	Standard-calorie formula milk (N= 43) or standard-calorie, protein-enriched formula milk (N= 41) or pooled donor term breast milk (N= 22). Feeds continued until a weight of 2.4 kg was attained or until infants were withdrawn from the study because of a "medical complication".
Outcomes	Time, from birth, to regain birth weight. Rate of weight change from birth and from point of regained birth weight.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Schultz 1980

Methods	1. Blinding of randomisation: Can't tell 2. Blinding of intervention: No 3. Complete follow up: Yes 4. Blinding of outcome measurement: Can't tell
Participants	20 preterm or low birth weight infants; all infants to be "physically normal with no further signs of disease; no further details published. Dept of Paediatrics, University Medical School, Pecs, Hungary, prior to 1980.
Interventions	Standard calorie protein-enriched formula milk (N= 10) versus pooled term donor breast milk (N= 10) for at least four weeks from birth.
Outcomes	Time, from birth, to regain birth weight (mean but no standard devaition or value to allow calculation of SD). Mean weight change from birth and from regaining birth weight calculable from graph but no SD.
Notes	No standard deviation for outcomes: the author will be contacted to request the relevant data.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Tyson 1983

Methods	1. Blinding of randomisation: Yes 2. Blinding of intervention: No 3. Complete follow up: Yes 4. Blinding of outcome measurement: Can't tell for growth assessments, yes for Brazelton score.
Participants	81 very low birth weight infants, excluding infants with "any significant illness" or those who required ventilatory support at day 10.

Tyson 1983 *(Continued)*

Interventions	Protein, calorie, and mineral-enriched formula milk (N=44) versus term human milk (N=37). Feeds were allocated on the tenth day of life, and continued until the infant reached a weight of 2000 g or until withdrawn from the study because of "any illness requiring intravenous infusion of fat or protein".
Outcomes	Mean daily rates of change in weight, crown-heel length and head circumference from the tenth until the thirtieth day of life were reported.
Notes	Adverse events, including necrotising enterocolitis reported as withdrawal criteria, rather than as outcomes.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Armand 1996	Although not clearly stated in the title or abstract, this was a non-randomised study.
Carey 1987	Although not clearly stated in the title or abstract, this was a non-randomised study.
Narayanan 1982	Human milk fed infants received a mixture of term and preterm milks: No comparison with exclusive feeding with term breast milk.
Putet 1984	Although not clearly stated in the title or abstract, feeds do not appear to have been randomly assigned.
Svenningsen 1982	No comparison with exclusive feeding with preterm breast milk.

DATA AND ANALYSES

Comparison 1. All formula milks versus term human milk

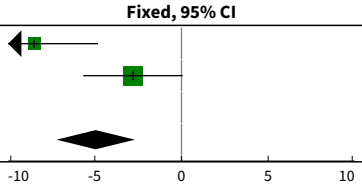
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Time to regain birth weight (days from birth)	2	146	Mean Difference (IV, Fixed, 95% CI)	-4.95 [-7.21, -2.69]
2 Short term weight change (g/day)	4	290	Mean Difference (IV, Fixed, 95% CI)	6.13 [4.93, 7.34]
3 Short term weight change (g/kg/day)	1	58	Mean Difference (IV, Fixed, 95% CI)	5.20 [2.85, 7.55]
4 Short term change in crown-heel length (mm/week)	4	210	Mean Difference (IV, Fixed, 95% CI)	1.71 [1.05, 2.38]

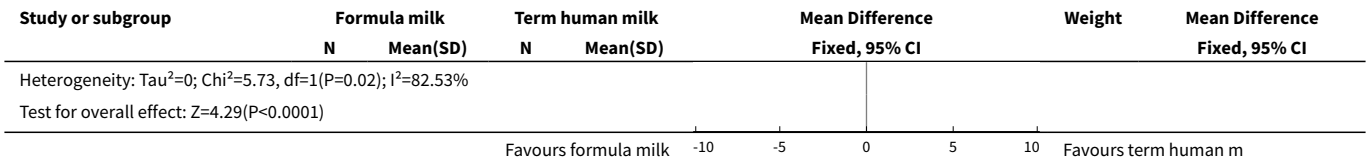
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5 Short term change in head circumference (mm/week)	4	232	Mean Difference (IV, Fixed, 95% CI)	1.58 [0.98, 2.19]
6 Feed intolerance or diarrhoea	2	128	Risk Ratio (M-H, Fixed, 95% CI)	3.28 [0.73, 14.76]
7 Necrotising enterocolitis	3	287	Risk Ratio (M-H, Fixed, 95% CI)	2.49 [0.85, 7.26]
8 Weight (kg) at 9 months post term	1	110	Mean Difference (IV, Fixed, 95% CI)	0.20 [-0.27, 0.67]
9 Length (cm) at 9 months post term	1	110	Mean Difference (IV, Fixed, 95% CI)	0.40 [-0.93, 1.73]
10 Head circumference (cm) at 9 months post term	1	110	Mean Difference (IV, Fixed, 95% CI)	0.20 [-0.45, 0.85]
11 Knobloch developmental quotient at 9 months	1	110	Mean Difference (IV, Fixed, 95% CI)	1.0 [-2.76, 4.76]
12 Knobloch adaptive score at 9 months	1	110	Mean Difference (IV, Fixed, 95% CI)	2.10 [-1.81, 6.01]
13 Knobloch gross motor score at 9 months	1	110	Mean Difference (IV, Fixed, 95% CI)	-0.20 [-6.09, 5.69]
14 Knobloch fine motor score at 9 months	1	110	Mean Difference (IV, Fixed, 95% CI)	1.90 [-3.03, 6.83]
15 Knobloch language score at 9 months	1	110	Mean Difference (IV, Fixed, 95% CI)	1.40 [-3.65, 6.45]
16 Knobloch personal-social score at 9 months	1	110	Mean Difference (IV, Fixed, 95% CI)	0.0 [-3.76, 3.76]
17 Neurological impairment at 9 months	1	122	Risk Ratio (M-H, Fixed, 95% CI)	2.36 [0.75, 7.42]
18 Neurological impairment at 18 months	1	122	Risk Ratio (M-H, Fixed, 95% CI)	2.06 [0.64, 6.68]
19 Bayley mental development index at 18 months	1	114	Mean Difference (IV, Fixed, 95% CI)	-3.10 [-9.81, 3.61]
20 Bayley psychomotor development index at 18 months	1	114	Mean Difference (IV, Fixed, 95% CI)	1.20 [-4.38, 6.78]
21 Subscapular skinfold thickness (mm) at 9 months post term	1	110	Mean Difference (IV, Fixed, 95% CI)	-0.20 [-0.74, 0.34]
22 Triceps skinfold thickness at 9 months post term	1	110	Mean Difference (IV, Fixed, 95% CI)	0.30 [-0.27, 0.87]
23 Body-mass index at 9 months post term	1	110	Mean Difference (IV, Fixed, 95% CI)	0.20 [-0.42, 0.82]
24 Weight (kg) at 18 months post term	1	136	Mean Difference (IV, Fixed, 95% CI)	0.10 [-0.37, 0.57]
25 Length (cm) at 18 months post term	1	136	Mean Difference (IV, Fixed, 95% CI)	0.60 [-0.68, 1.88]
26 Head circumference (cm) at 18 months post term	1	136	Mean Difference (IV, Fixed, 95% CI)	0.10 [-0.44, 0.64]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
27 Subscapular skinfold thickness (mm) at 18 months post term	1	136	Mean Difference (IV, Fixed, 95% CI)	-0.20 [-0.60, 0.20]
28 Triceps skinfold thickness (mm) at 18 months post term	1	136	Mean Difference (IV, Fixed, 95% CI)	-0.10 [-0.69, 0.49]
29 Body mass index at 18 months post term	1	136	Mean Difference (IV, Fixed, 95% CI)	-0.10 [-0.62, 0.42]
30 Weight (kg) at 7.5-8 years of age	1	130	Mean Difference (IV, Fixed, 95% CI)	0.5 [-1.24, 2.24]
31 Length (cm) at 7.5-8 years of age	1	130	Mean Difference (IV, Fixed, 95% CI)	1.0 [-1.26, 3.26]
32 Head circumference (cm) at 7.5-8 years of age	1	130	Mean Difference (IV, Fixed, 95% CI)	0.10 [-0.56, 0.76]
33 Subscapular skinfold thickness (mm) at 7.5-8 years of age	1	130	Mean Difference (IV, Fixed, 95% CI)	0.60 [-0.33, 1.53]
34 Triceps skinfold thickness (mm) at 7.5-8 years of age	1	130	Mean Difference (IV, Fixed, 95% CI)	0.30 [-0.82, 1.42]
35 Body mass index at 7.5-8 years of age	1	130	Mean Difference (IV, Fixed, 95% CI)	0.0 [-0.92, 0.92]
36 Short term change in crown-rump length (mm/week)	1	106	Mean Difference (IV, Fixed, 95% CI)	0.60 [0.09, 1.11]
37 Short term change in femoral length (mm/week)	1	106	Mean Difference (IV, Fixed, 95% CI)	0.40 [0.20, 0.60]
38 Short term change in triceps skinfold thickness (mm/week)	1	76	Mean Difference (IV, Fixed, 95% CI)	0.14 [0.01, 0.27]
39 Brazelton Neonatal Behavioural Assessment Scale (response to auditory and visual stimuli)	1	76	Mean Difference (IV, Fixed, 95% CI)	0.80 [0.26, 1.34]
40 Brazelton Neonatal Behavioural Assessment Scale (response to inanimate objects)	1	76	Mean Difference (IV, Fixed, 95% CI)	2.5 [1.35, 3.65]

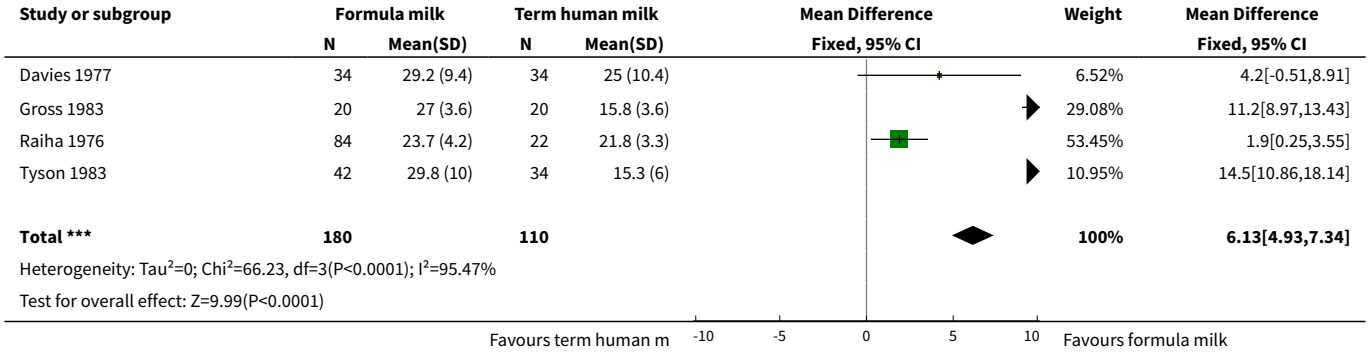
Analysis 1.1. Comparison 1 All formula milks versus term human milk, Outcome 1 Time to regain birth weight (days from birth).

Study or subgroup	Formula milk N	Formula milk Mean(SD)	Term human milk N	Term human milk Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Gross 1983	20	10.3 (3.6)	20	18.8 (7.6)		37.69%	-8.5[-12.19,-4.81]
Raiha 1976	84	13.5 (5.3)	22	16.3 (6.3)		62.31%	-2.8[-5.67,0.07]
Total ***	**104**		**42**			**100%**	**-4.95[-7.21,-2.69]**

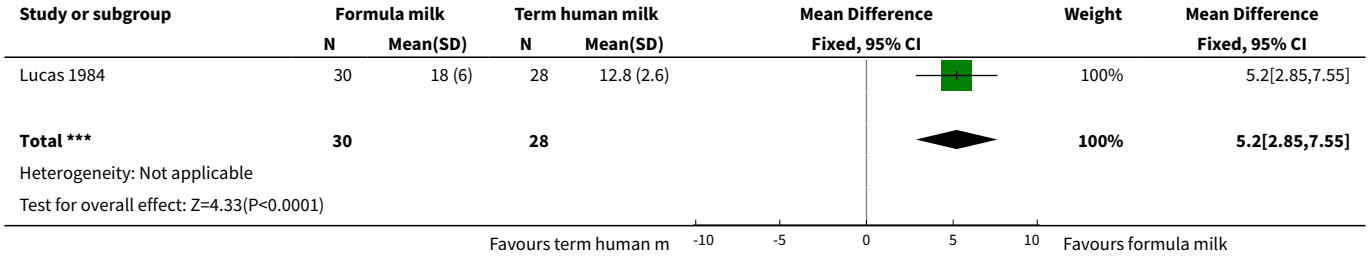




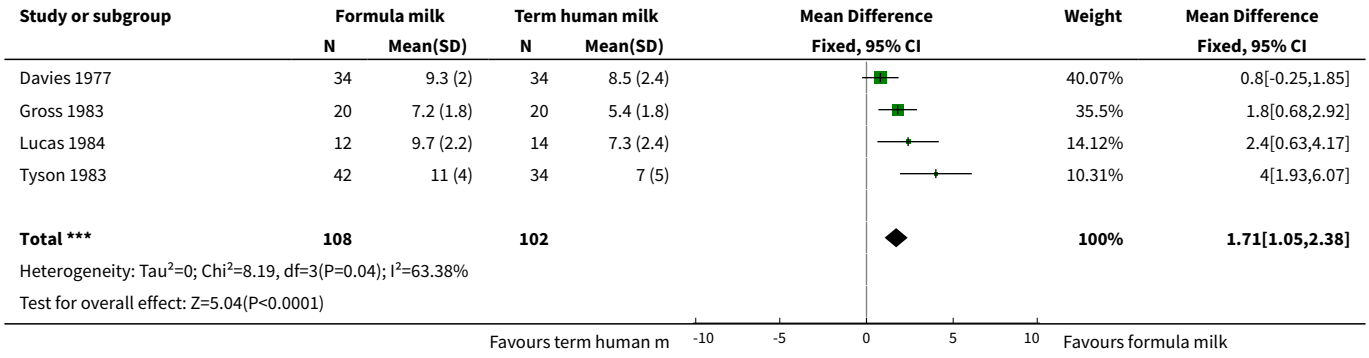
Analysis 1.2. Comparison 1 All formula milks versus term human milk, Outcome 2 Short term weight change (g/day).



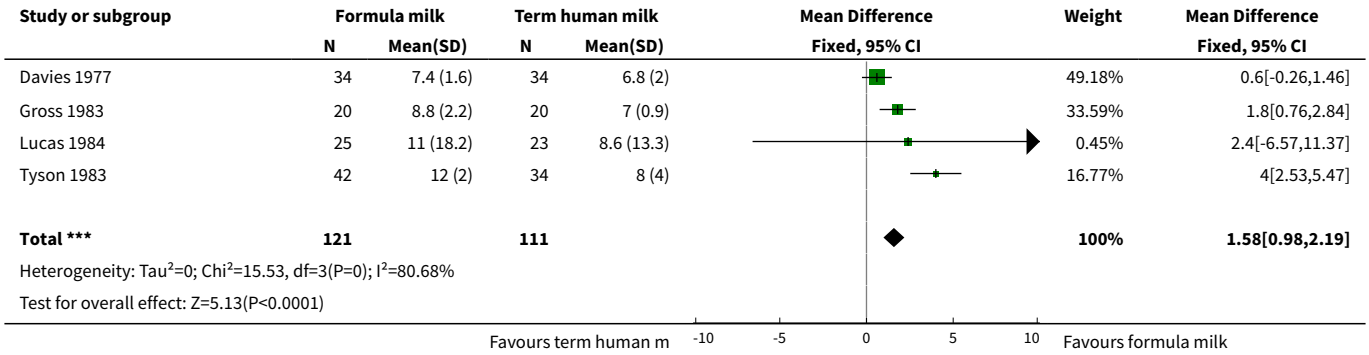
Analysis 1.3. Comparison 1 All formula milks versus term human milk, Outcome 3 Short term weight change (g/kg/day).



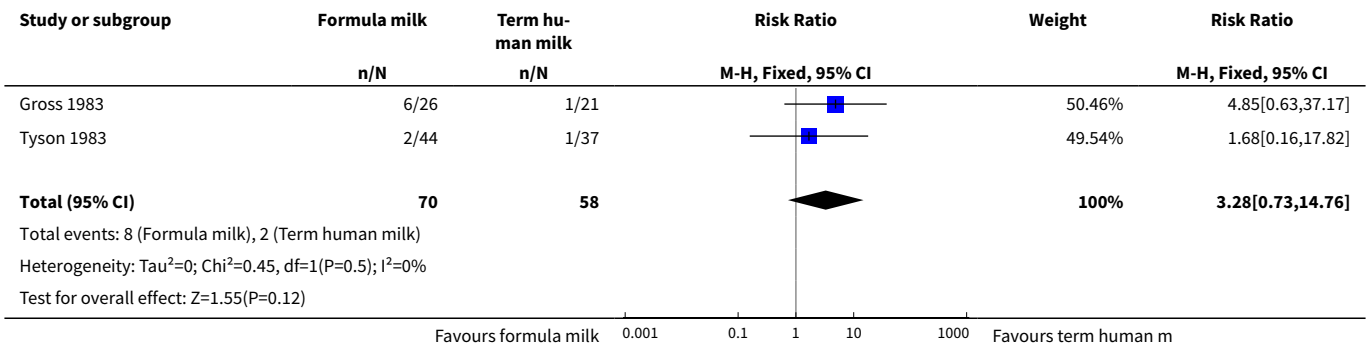
Analysis 1.4. Comparison 1 All formula milks versus term human milk, Outcome 4 Short term change in crown-heel length (mm/week).



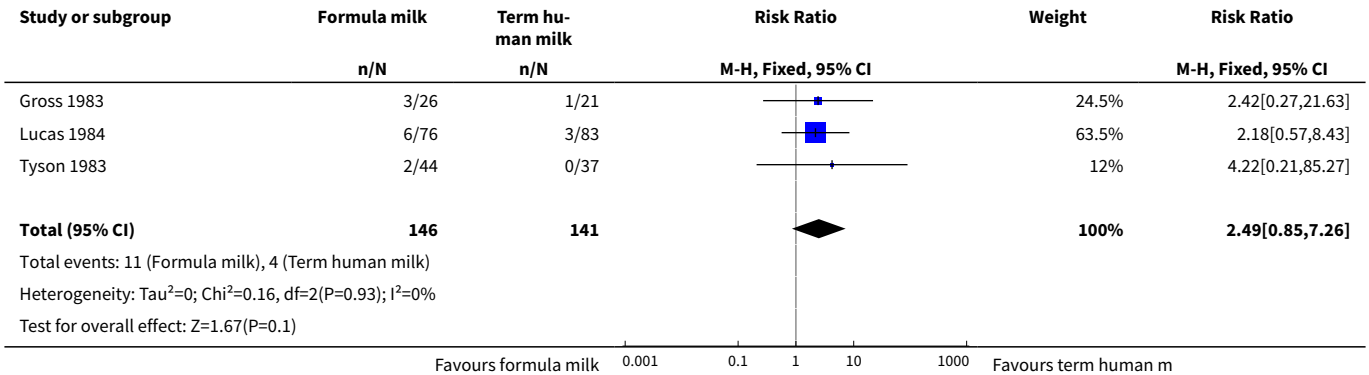
Analysis 1.5. Comparison 1 All formula milks versus term human milk, Outcome 5 Short term change in head circumference (mm/week).



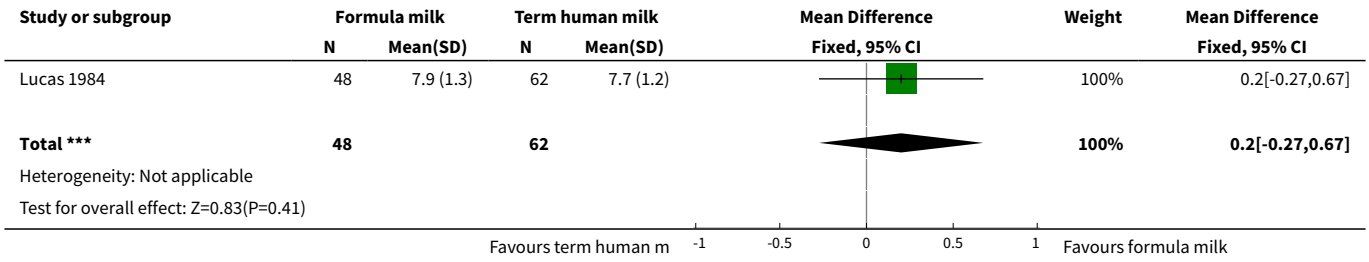
Analysis 1.6. Comparison 1 All formula milks versus term human milk, Outcome 6 Feed intolerance or diarrhoea.



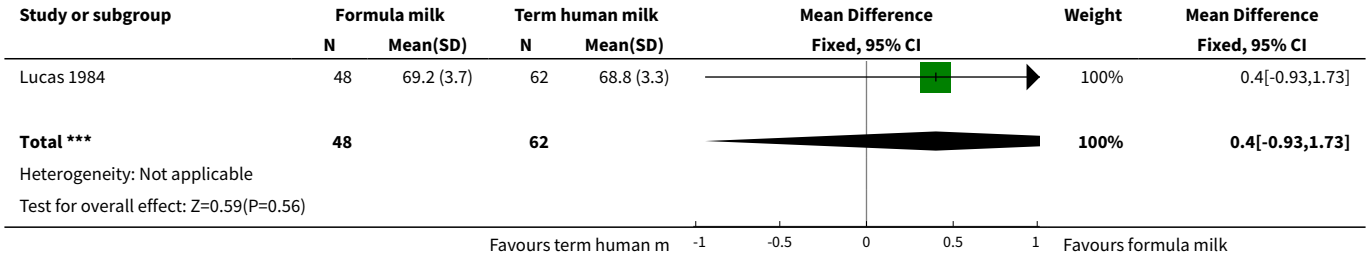
Analysis 1.7. Comparison 1 All formula milks versus term human milk, Outcome 7 Necrotising enterocolitis.



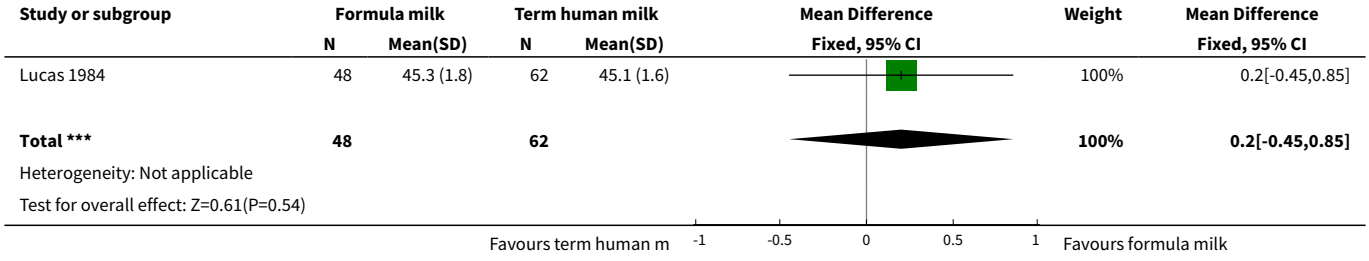
Analysis 1.8. Comparison 1 All formula milks versus term human milk, Outcome 8 Weight (kg) at 9 months post term.



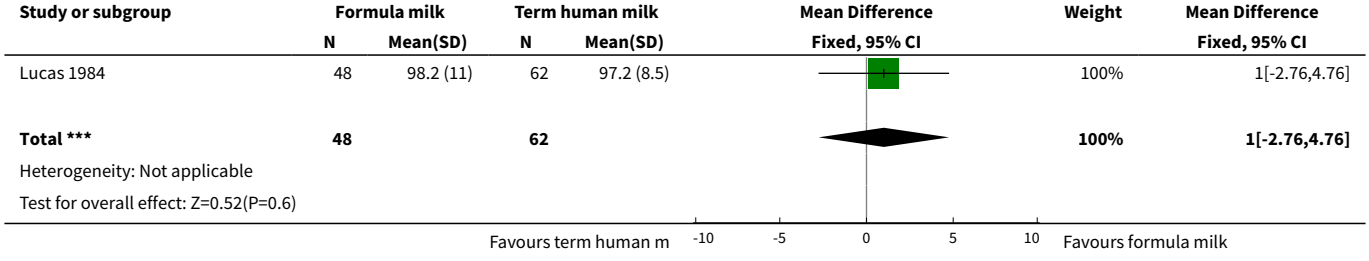
Analysis 1.9. Comparison 1 All formula milks versus term human milk, Outcome 9 Length (cm) at 9 months post term.



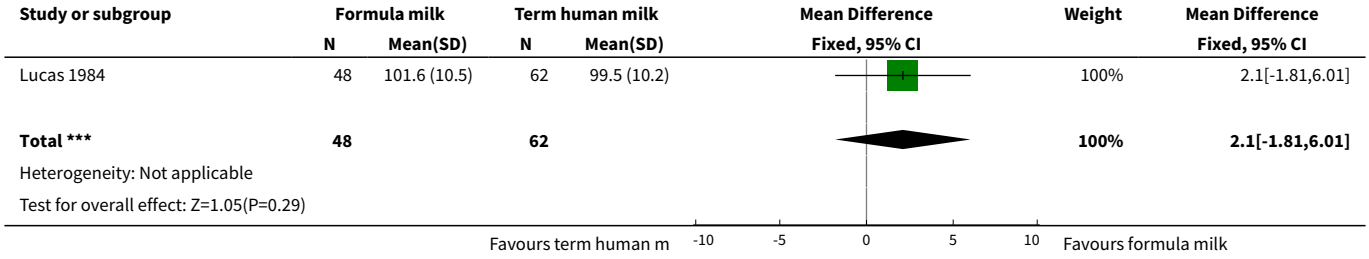
Analysis 1.10. Comparison 1 All formula milks versus term human milk, Outcome 10 Head circumference (cm) at 9 months post term.



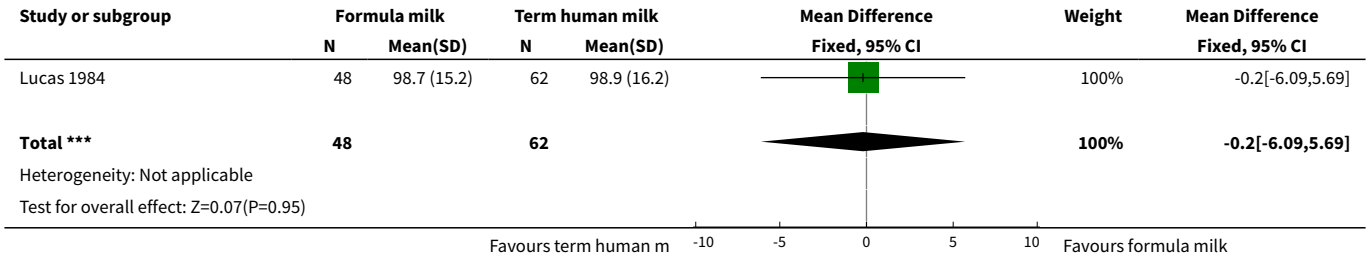
Analysis 1.11. Comparison 1 All formula milks versus term human milk, Outcome 11 Knobloch developmental quotient at 9 months.



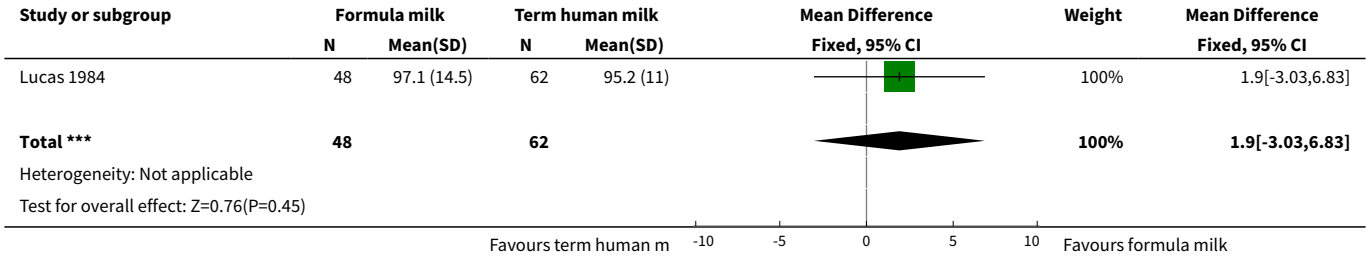
Analysis 1.12. Comparison 1 All formula milks versus term human milk, Outcome 12 Knobloch adaptive score at 9 months.



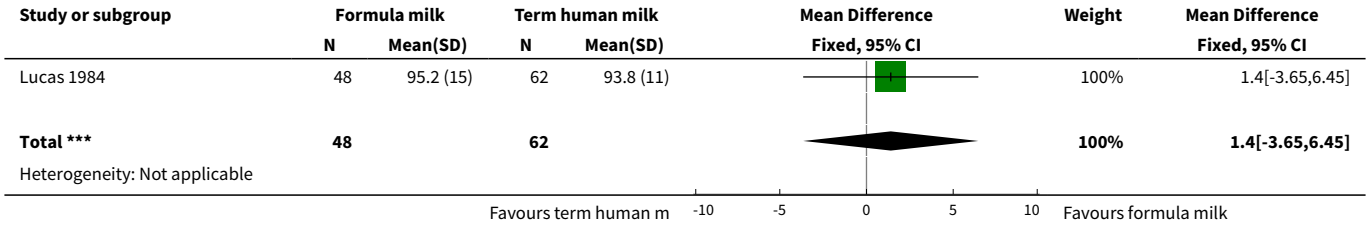
Analysis 1.13. Comparison 1 All formula milks versus term human milk, Outcome 13 Knobloch gross motor score at 9 months.

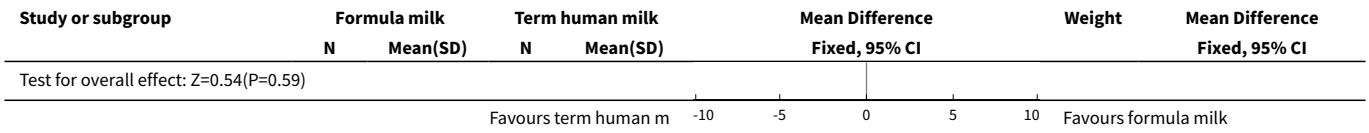


Analysis 1.14. Comparison 1 All formula milks versus term human milk, Outcome 14 Knobloch fine motor score at 9 months.

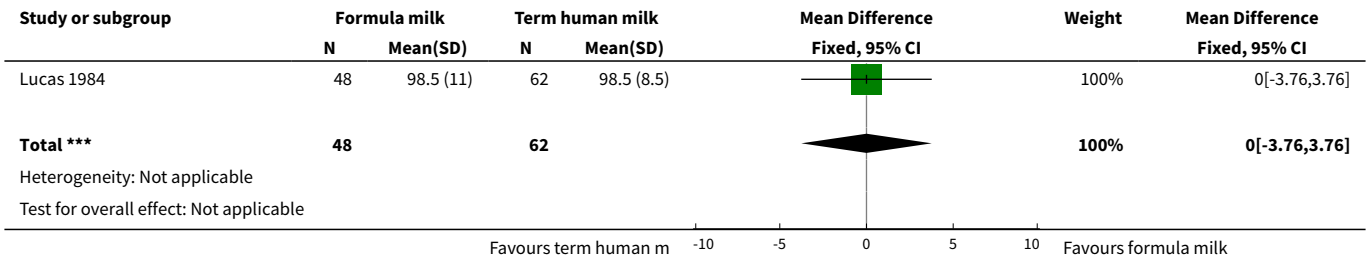


Analysis 1.15. Comparison 1 All formula milks versus term human milk, Outcome 15 Knobloch language score at 9 months.

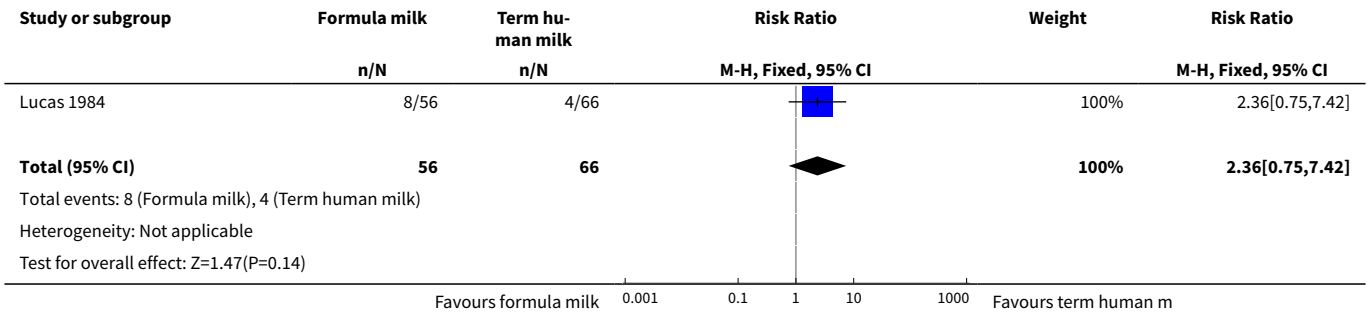




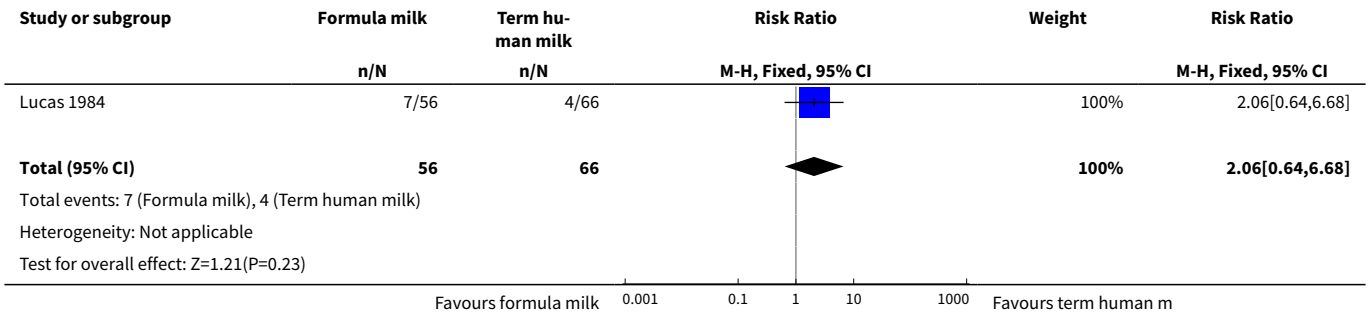
Analysis 1.16. Comparison 1 All formula milks versus term human milk, Outcome 16 Knobloch personal-social score at 9 months.



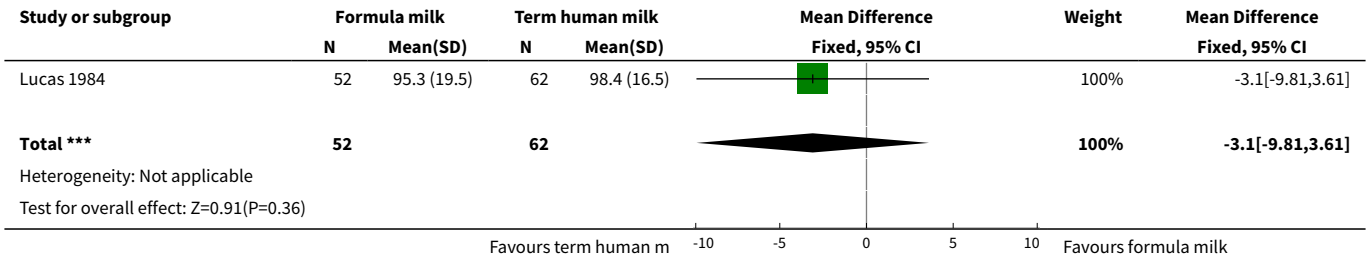
Analysis 1.17. Comparison 1 All formula milks versus term human milk, Outcome 17 Neurological impairment at 9 months.



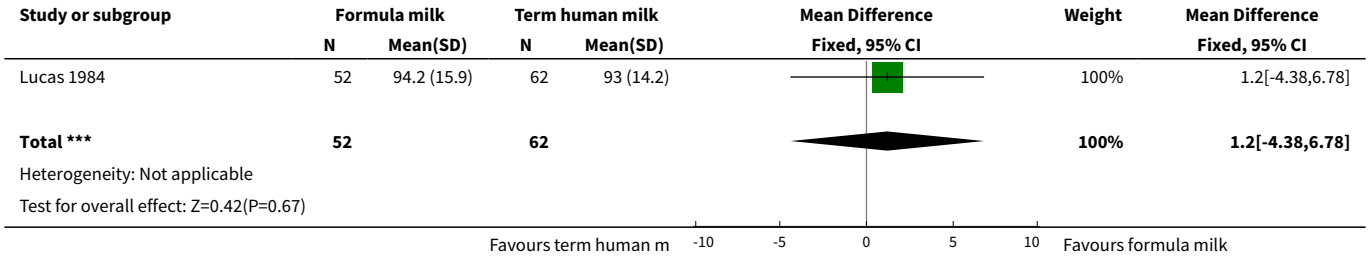
Analysis 1.18. Comparison 1 All formula milks versus term human milk, Outcome 18 Neurological impairment at 18 months.



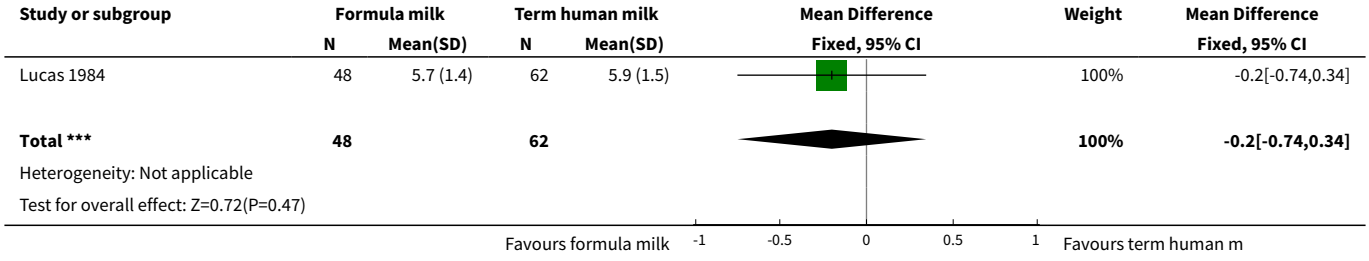
Analysis 1.19. Comparison 1 All formula milks versus term human milk, Outcome 19 Bayley mental development index at 18 months.



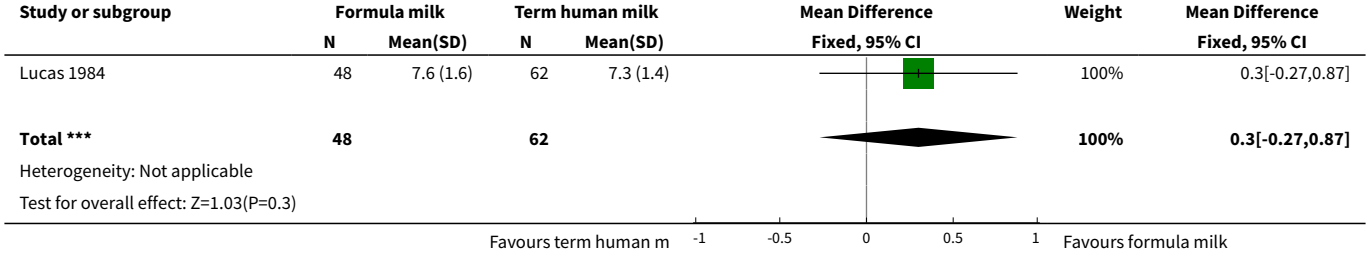
Analysis 1.20. Comparison 1 All formula milks versus term human milk, Outcome 20 Bayley psychomotor development index at 18 months.



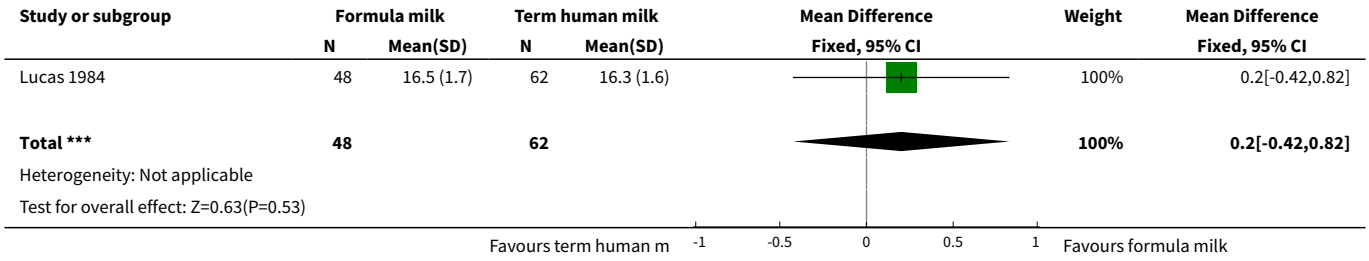
Analysis 1.21. Comparison 1 All formula milks versus term human milk, Outcome 21 Subscapular skinfold thickness (mm) at 9 months post term.



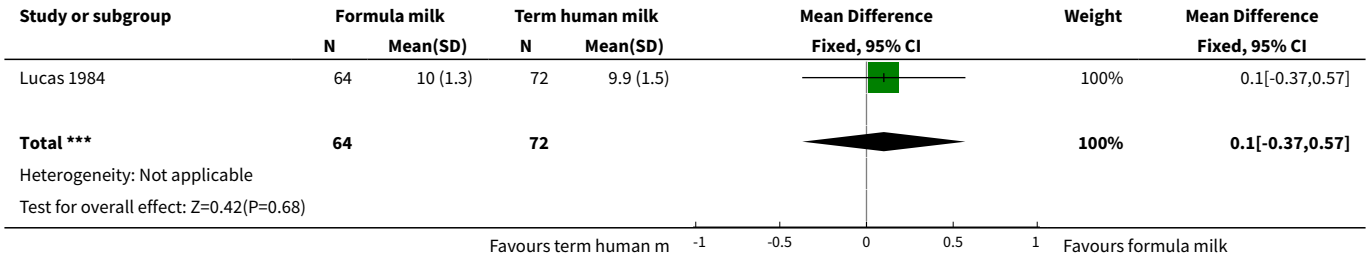
Analysis 1.22. Comparison 1 All formula milks versus term human milk, Outcome 22 Triceps skinfold thickness at 9 months post term.



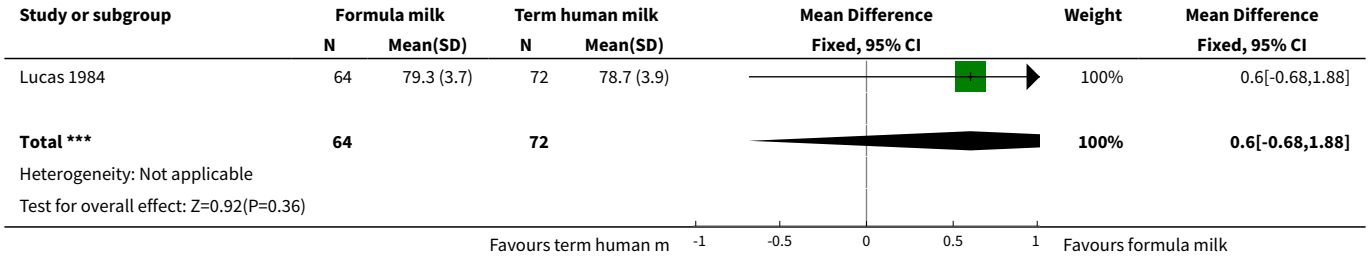
Analysis 1.23. Comparison 1 All formula milks versus term human milk, Outcome 23 Body-mass index at 9 months post term.



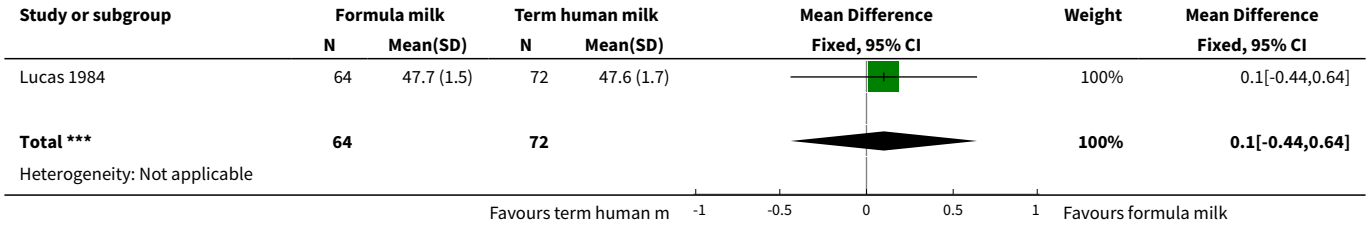
Analysis 1.24. Comparison 1 All formula milks versus term human milk, Outcome 24 Weight (kg) at 18 months post term.

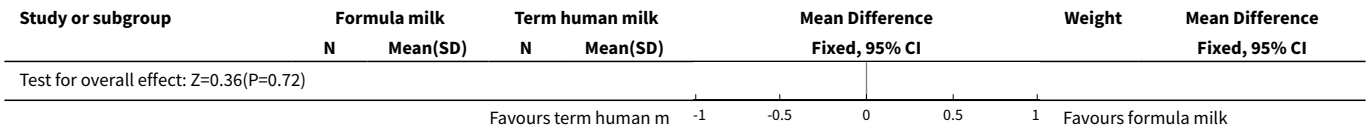


Analysis 1.25. Comparison 1 All formula milks versus term human milk, Outcome 25 Length (cm) at 18 months post term.

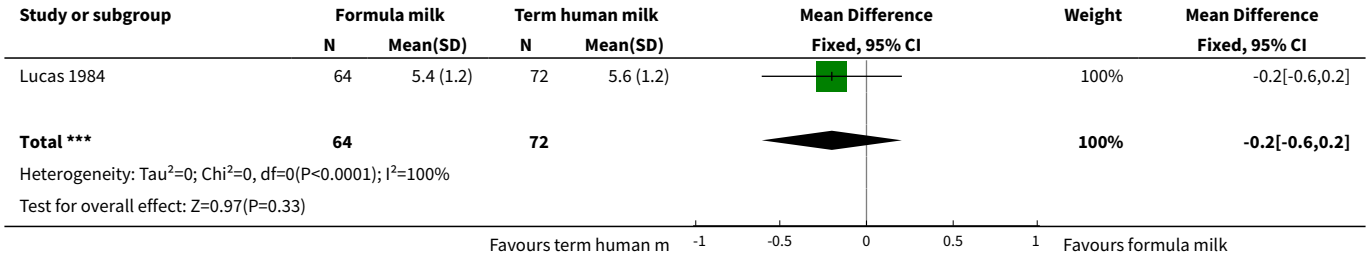


Analysis 1.26. Comparison 1 All formula milks versus term human milk, Outcome 26 Head circumference (cm) at 18 months post term.

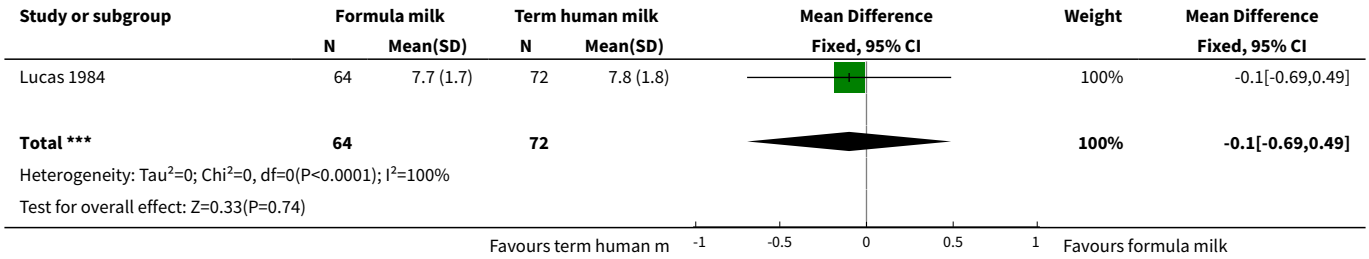




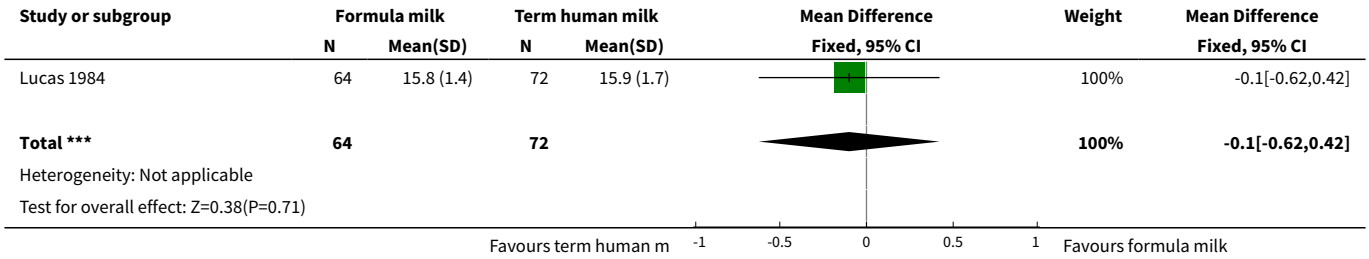
Analysis 1.27. Comparison 1 All formula milks versus term human milk, Outcome 27 Subscapular skinfold thickness (mm) at 18 months post term.



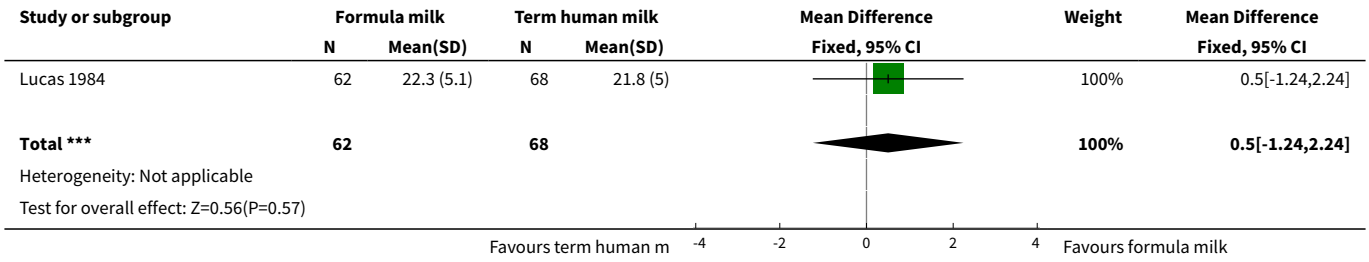
Analysis 1.28. Comparison 1 All formula milks versus term human milk, Outcome 28 Triceps skinfold thickness (mm) at 18 months post term.



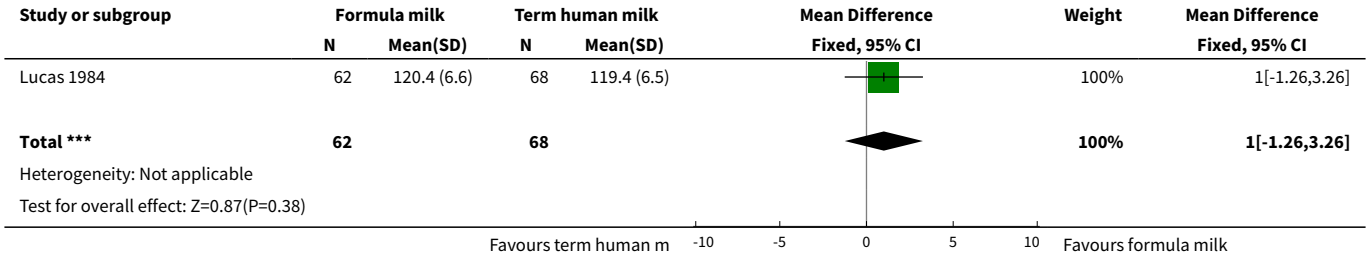
Analysis 1.29. Comparison 1 All formula milks versus term human milk, Outcome 29 Body mass index at 18 months post term.



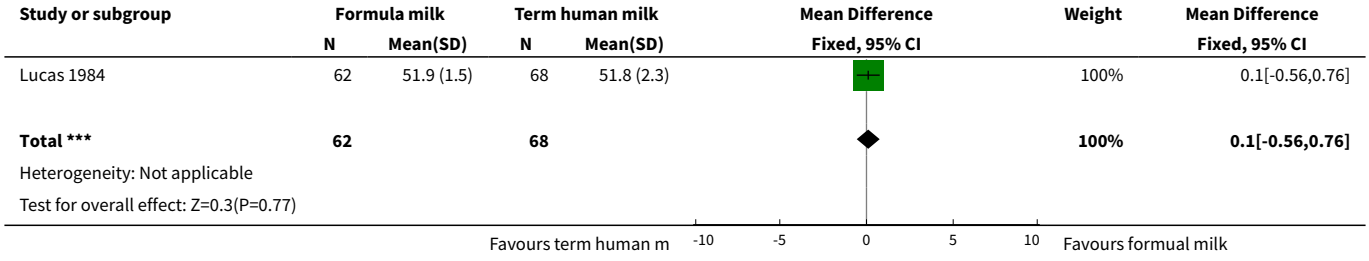
Analysis 1.30. Comparison 1 All formula milks versus term human milk, Outcome 30 Weight (kg) at 7.5-8 years of age.



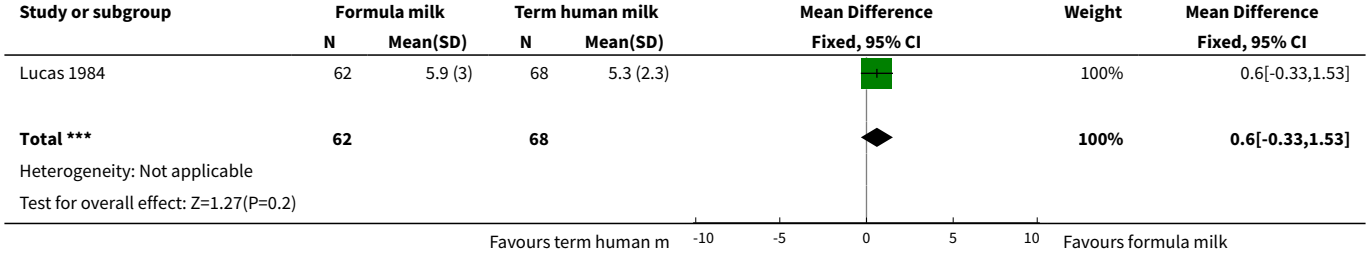
Analysis 1.31. Comparison 1 All formula milks versus term human milk, Outcome 31 Length (cm) at 7.5-8 years of age.



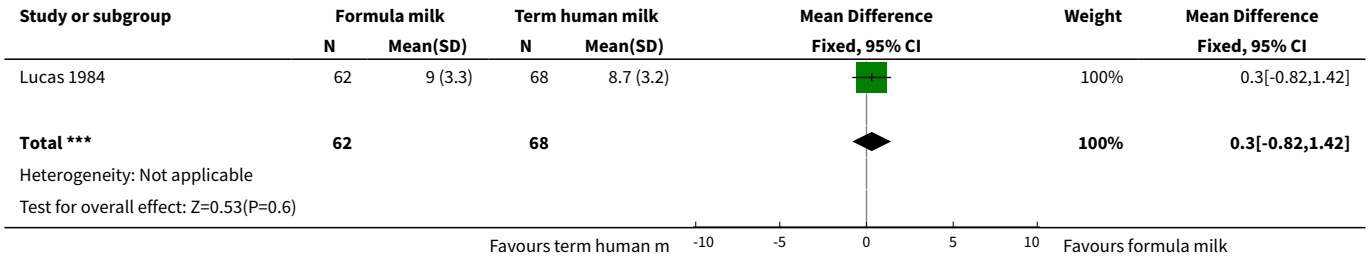
Analysis 1.32. Comparison 1 All formula milks versus term human milk, Outcome 32 Head circumference (cm) at 7.5-8 years of age.



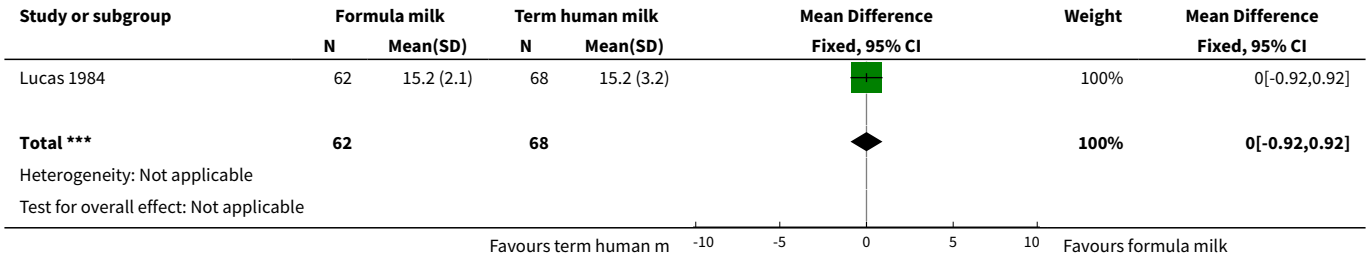
Analysis 1.33. Comparison 1 All formula milks versus term human milk, Outcome 33 Subscapular skinfold thickness (mm) at 7.5-8 years of age.



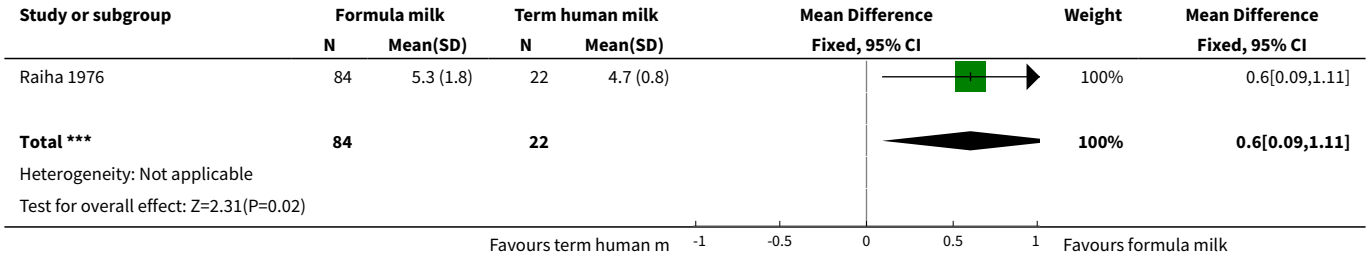
Analysis 1.34. Comparison 1 All formula milks versus term human milk, Outcome 34 Triceps skinfold thickness (mm) at 7.5-8 years of age.



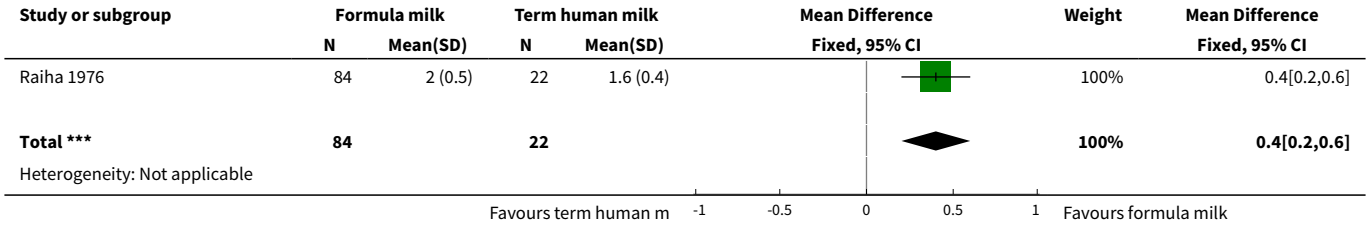
Analysis 1.35. Comparison 1 All formula milks versus term human milk, Outcome 35 Body mass index at 7.5-8 years of age.



Analysis 1.36. Comparison 1 All formula milks versus term human milk, Outcome 36 Short term change in crown-rump length (mm/week).



Analysis 1.37. Comparison 1 All formula milks versus term human milk, Outcome 37 Short term change in femoral length (mm/week).

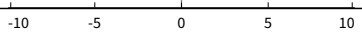


Study or subgroup	Formula milk N	Formula milk Mean(SD)	Term human milk N	Term human milk Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Test for overall effect: Z=3.95(P<0.0001)							

Favours term human m Favours formula milk

Analysis 1.38. Comparison 1 All formula milks versus term human milk, Outcome 38 Short term change in triceps skinfold thickness (mm/week).

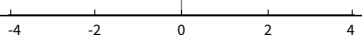
Study or subgroup	Formula milk N	Formula milk Mean(SD)	Term human milk N	Term human milk Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Tyson 1983	42	0.5 (0.3)	34	0.3 (0.3)		100%	0.14[0.01,0.27]
Total ***	**42**		**34**			**100%**	**0.14[0.01,0.27]**
Heterogeneity: Not applicable							
Test for overall effect: Z=2.03(P=0.04)							



Favours term human m Favours formula milk

Analysis 1.39. Comparison 1 All formula milks versus term human milk, Outcome 39 Brazelton Neonatal Behavioural Assessment Scale (response to auditory and visual stimuli).

Study or subgroup	Formula milk N	Formula milk Mean(SD)	Term human milk N	Term human milk Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Tyson 1983	42	3.4 (1.4)	34	2.6 (1)		100%	0.8[0.26,1.34]
Total ***	**42**		**34**			**100%**	**0.8[0.26,1.34]**
Heterogeneity: Tau²=0; Chi²=0, df=0(P<0.0001); I²=100%							
Test for overall effect: Z=2.9(P=0)							



Favours term human m Favours formula milk

Analysis 1.40. Comparison 1 All formula milks versus term human milk, Outcome 40 Brazelton Neonatal Behavioural Assessment Scale (response to inanimate objects).

Study or subgroup	Formula milk N	Formula milk Mean(SD)	Term human milk N	Term human milk Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Tyson 1983	42	7.5 (3)	34	5 (2.1)		100%	2.5[1.35,3.65]
Total ***	**42**		**34**			**100%**	**2.5[1.35,3.65]**
Heterogeneity: Not applicable							
Test for overall effect: Z=4.26(P<0.0001)							

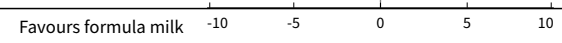
Favours term human m Favours formula milk

Comparison 2. Standard-calorie formula versus term human milk

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Time to regain birth weight (days from birth)	1	65	Mean Difference (IV, Fixed, 95% CI)	-3.0 [-6.15, 0.15]
2 Short term weight change (g/day)	1	65	Mean Difference (IV, Fixed, 95% CI)	2.30 [0.41, 4.19]
3 Short term change in crown-rump length (mm/week)	1	65	Mean Difference (IV, Fixed, 95% CI)	0.60 [-0.32, 1.52]
4 Short term change in femoral length (mm/week)	1	65	Mean Difference (IV, Fixed, 95% CI)	0.30 [0.08, 0.52]

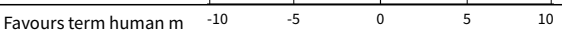
Analysis 2.1. Comparison 2 Standard-calorie formula versus term human milk, Outcome 1 Time to regain birth weight (days from birth).

Study or subgroup	Formula milk N	Formula milk Mean(SD)	Term human milk N	Term human milk Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Raiha 1976	43	13.3 (5.8)	22	16.3 (6.3)		100%	-3[-6.15,0.15]
Total ***	**43**		**22**			**100%**	**-3[-6.15,0.15]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.87(P=0.06)							



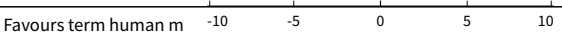
Analysis 2.2. Comparison 2 Standard-calorie formula versus term human milk, Outcome 2 Short term weight change (g/day).

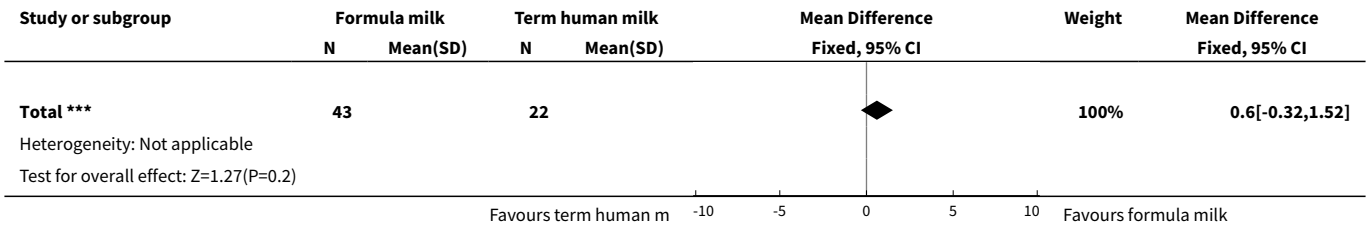
Study or subgroup	Formula milk N	Formula milk Mean(SD)	Term human milk N	Term human milk Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Raiha 1976	43	24.1 (4.3)	22	21.8 (3.3)		100%	2.3[0.41,4.19]
Total ***	**43**		**22**			**100%**	**2.3[0.41,4.19]**
Heterogeneity: Not applicable							
Test for overall effect: Z=2.39(P=0.02)							



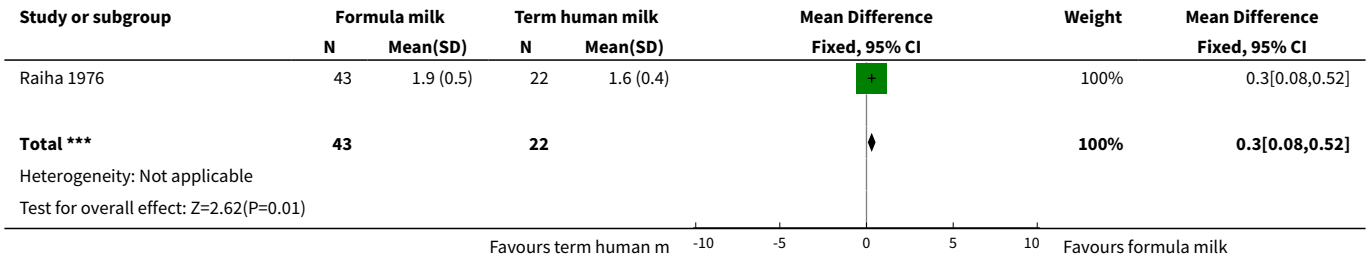
Analysis 2.3. Comparison 2 Standard-calorie formula versus term human milk, Outcome 3 Short term change in crown-rump length (mm/week).

Study or subgroup	Formula milk N	Formula milk Mean(SD)	Term human milk N	Term human milk Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Raiha 1976	43	5.6 (1.8)	22	5 (1.8)		100%	0.6[-0.32,1.52]





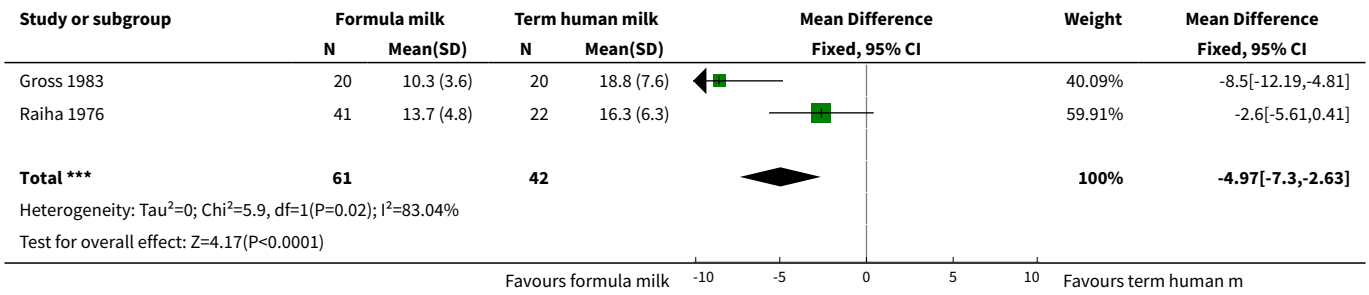
Analysis 2.4. Comparison 2 Standard-calorie formula versus term human milk, Outcome 4 Short term change in femoral length (mm/week).



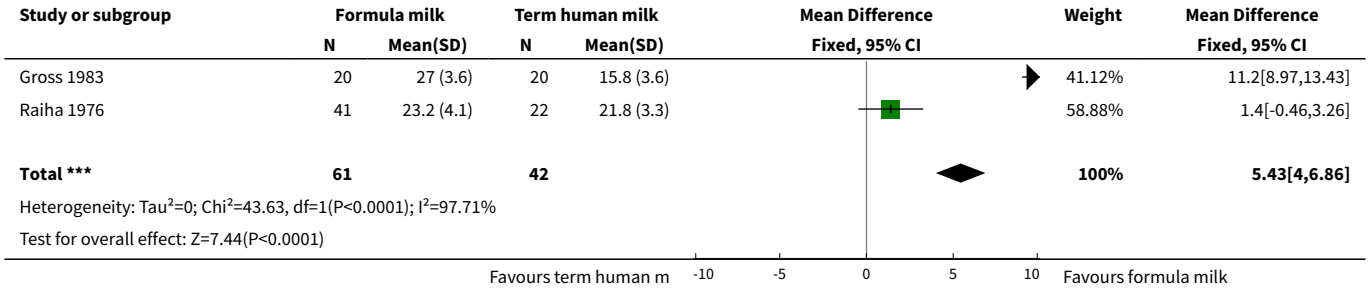
Comparison 3. Standard-calorie, protein-enriched formula versus term human milk

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Time to regain birth weight (days from birth)	2	103	Mean Difference (IV, Fixed, 95% CI)	-4.97 [-7.30, -2.63]
2 Short term weight change (g/day)	2	103	Mean Difference (IV, Fixed, 95% CI)	5.43 [4.00, 6.86]
3 Short term change in crown-heel length (mm/week)	1	40	Mean Difference (IV, Fixed, 95% CI)	1.80 [0.68, 2.92]
4 Short term change in head circumference (mm/week)	1	40	Mean Difference (IV, Fixed, 95% CI)	1.80 [0.76, 2.84]
5 Short term change in crown rump length (mm/week)	1	63	Mean Difference (IV, Fixed, 95% CI)	0.30 [-0.34, 0.94]
6 Short term change in femoral length (mm/week)	1	63	Mean Difference (IV, Fixed, 95% CI)	0.5 [0.27, 0.73]
7 Feed intolerance or diarrhoea	1	47	Risk Ratio (M-H, Fixed, 95% CI)	4.85 [0.63, 37.17]
8 Necrotising enterocolitis	1	47	Risk Ratio (M-H, Fixed, 95% CI)	2.42 [0.27, 21.63]

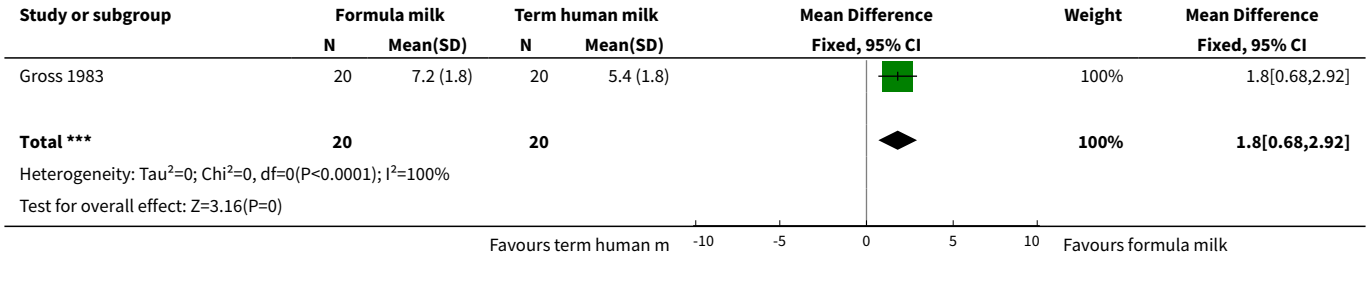
Analysis 3.1. Comparison 3 Standard-calorie, protein-enriched formula versus term human milk, Outcome 1 Time to regain birth weight (days from birth).



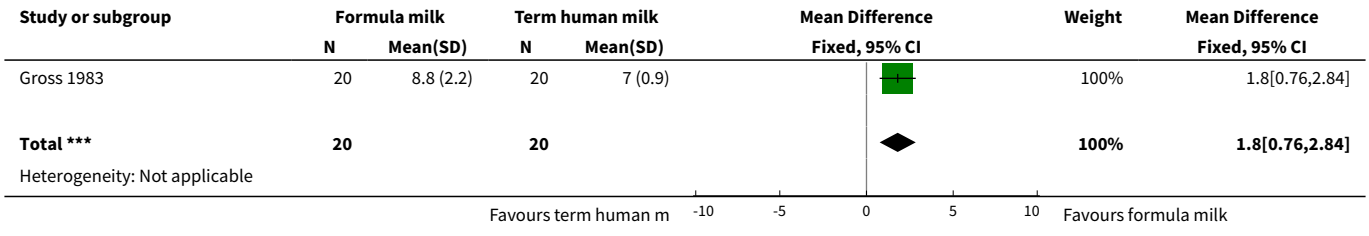
Analysis 3.2. Comparison 3 Standard-calorie, protein-enriched formula versus term human milk, Outcome 2 Short term weight change (g/day).

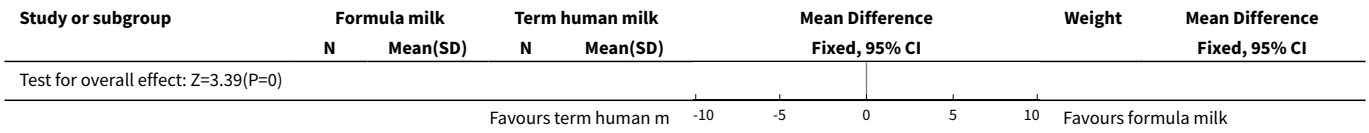


Analysis 3.3. Comparison 3 Standard-calorie, protein-enriched formula versus term human milk, Outcome 3 Short term change in crown-heel length (mm/week).

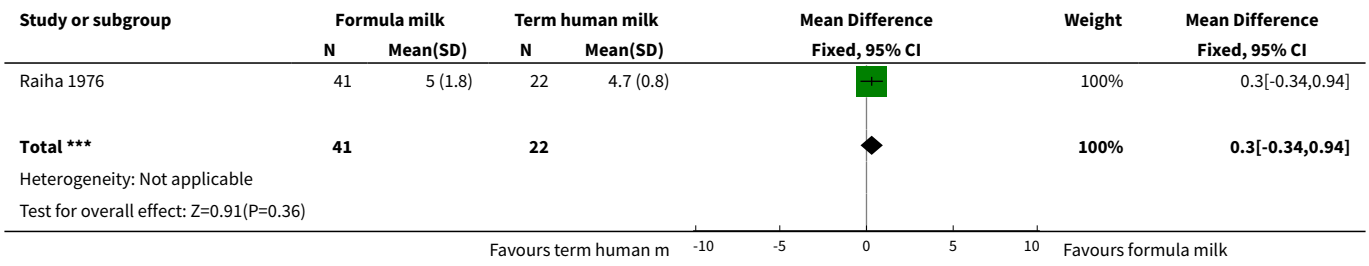


Analysis 3.4. Comparison 3 Standard-calorie, protein-enriched formula versus term human milk, Outcome 4 Short term change in head circumference (mm/week).

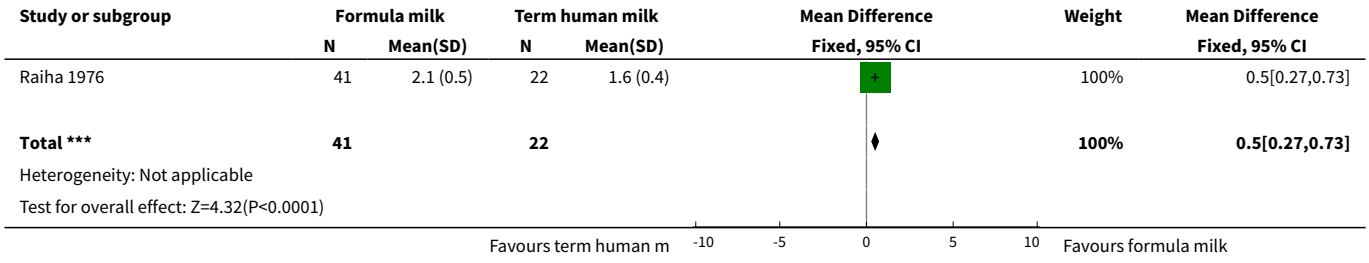




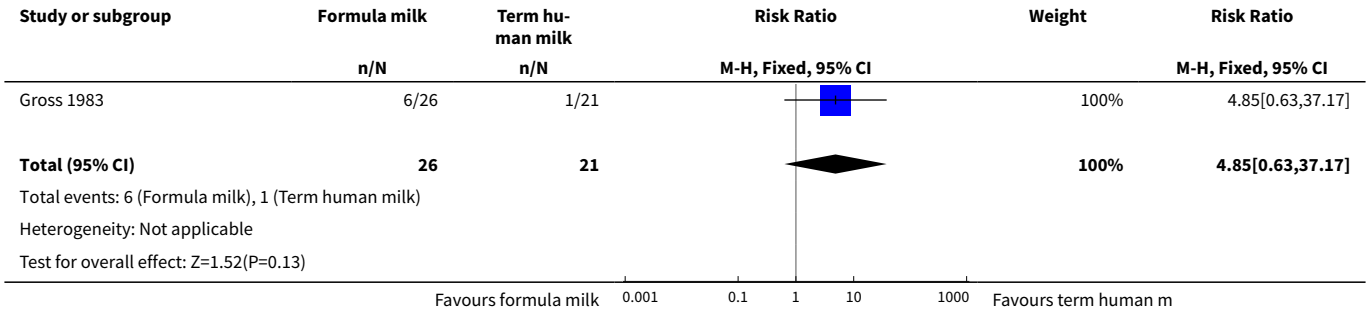
Analysis 3.5. Comparison 3 Standard-calorie, protein-enriched formula versus term human milk, Outcome 5 Short term change in crown rump length (mm/week).



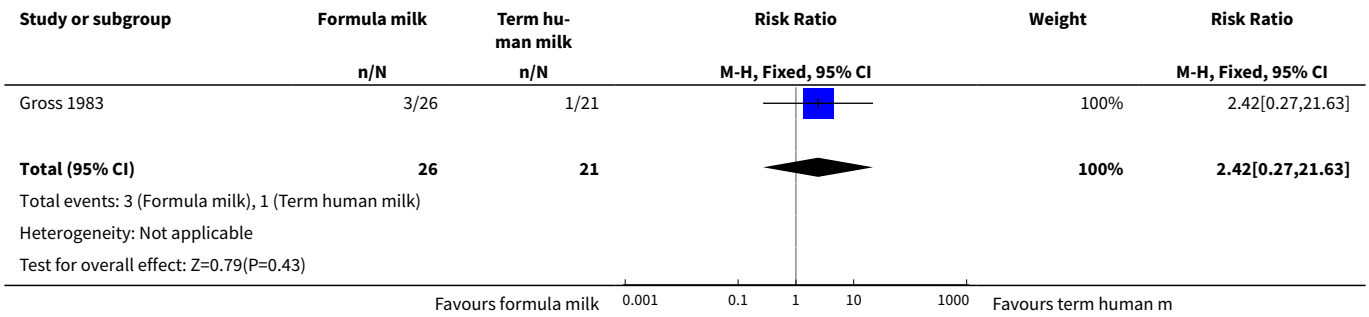
Analysis 3.6. Comparison 3 Standard-calorie, protein-enriched formula versus term human milk, Outcome 6 Short term change in femoral length (mm/week).



Analysis 3.7. Comparison 3 Standard-calorie, protein-enriched formula versus term human milk, Outcome 7 Feed intolerance or diarrhoea.



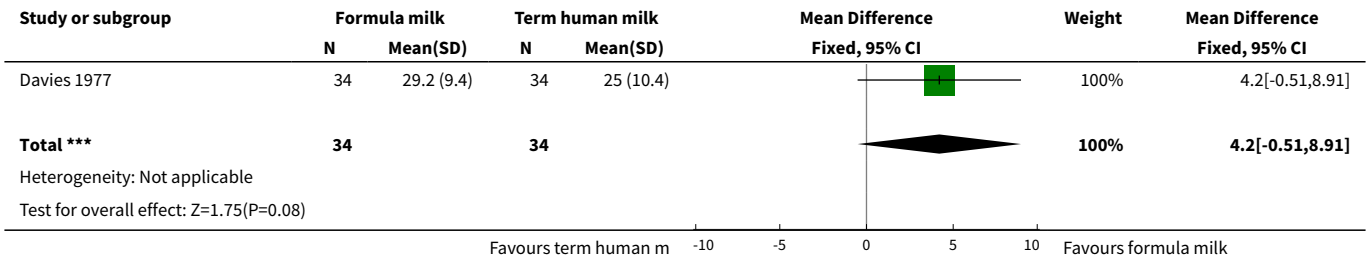
Analysis 3.8. Comparison 3 Standard-calorie, protein-enriched formula versus term human milk, Outcome 8 Necrotising enterocolitis.



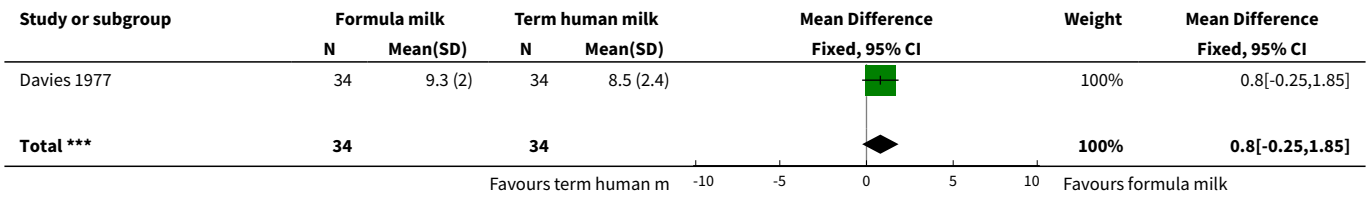
Comparison 4. Standard-calorie, protein-enriched and mineral-supplemented formula versus term human milk

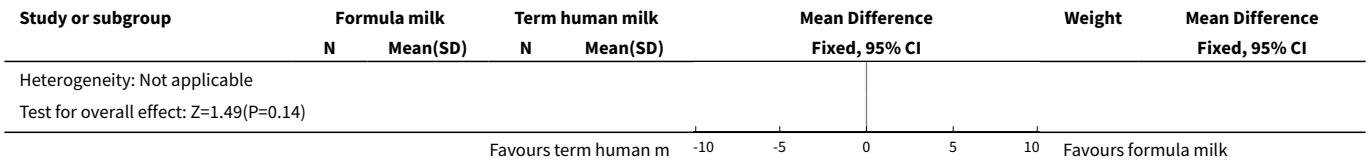
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Short term weight change (g/day)	1	68	Mean Difference (IV, Fixed, 95% CI)	4.20 [-0.51, 8.91]
2 Short term change in crown-heel length	1	68	Mean Difference (IV, Fixed, 95% CI)	0.80 [-0.25, 1.85]
3 Short term change in head circumference (mm/week)	1	68	Mean Difference (IV, Fixed, 95% CI)	0.60 [-0.26, 1.46]

Analysis 4.1. Comparison 4 Standard-calorie, protein-enriched and mineral-supplemented formula versus term human milk, Outcome 1 Short term weight change (g/day).

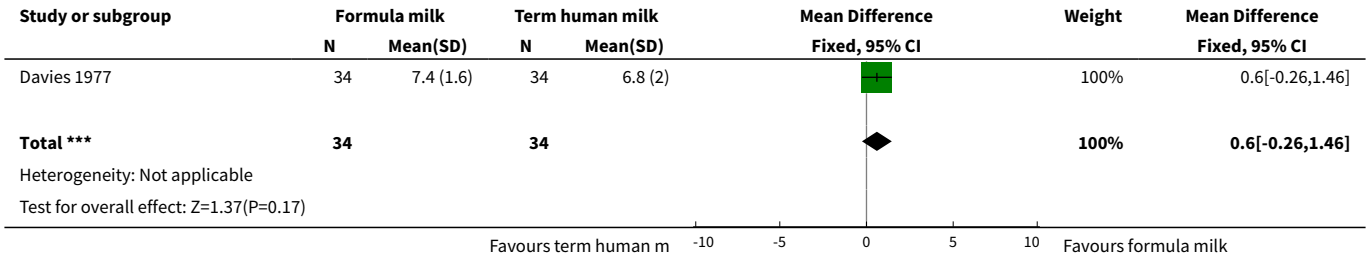


Analysis 4.2. Comparison 4 Standard-calorie, protein-enriched and mineral-supplemented formula versus term human milk, Outcome 2 Short term change in crown-heel length.





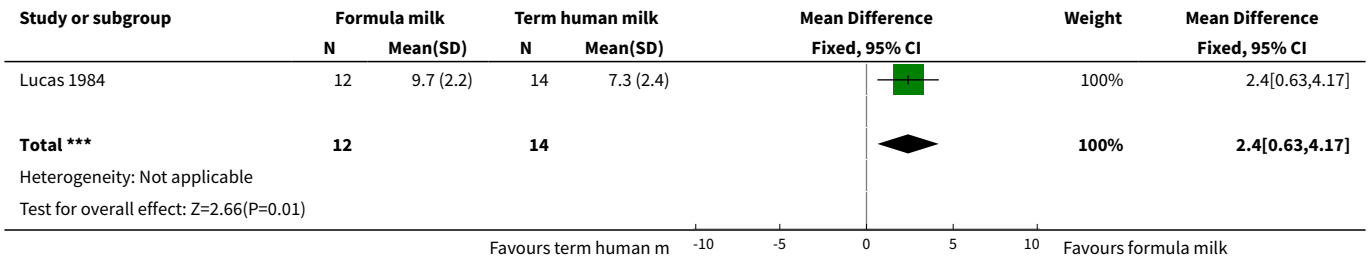
Analysis 4.3. Comparison 4 Standard-calorie, protein-enriched and mineral-supplemented formula versus term human milk, Outcome 3 Short term change in head circumference (mm/week).



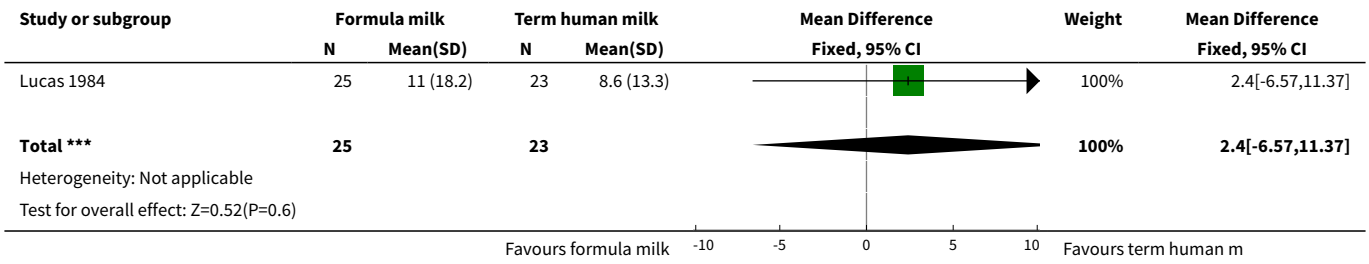
Comparison 5. Calorie-supplemented, protein-enriched formula versus term human milk

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Short term change in crown-heel length (mm/week)	1	26	Mean Difference (IV, Fixed, 95% CI)	2.40 [0.63, 4.17]
2 Short term change in head circumference (mm/week)	1	48	Mean Difference (IV, Fixed, 95% CI)	2.40 [-6.57, 11.37]
3 Necrotising enterocolitis	1	159	Risk Ratio (M-H, Fixed, 95% CI)	2.18 [0.57, 8.43]

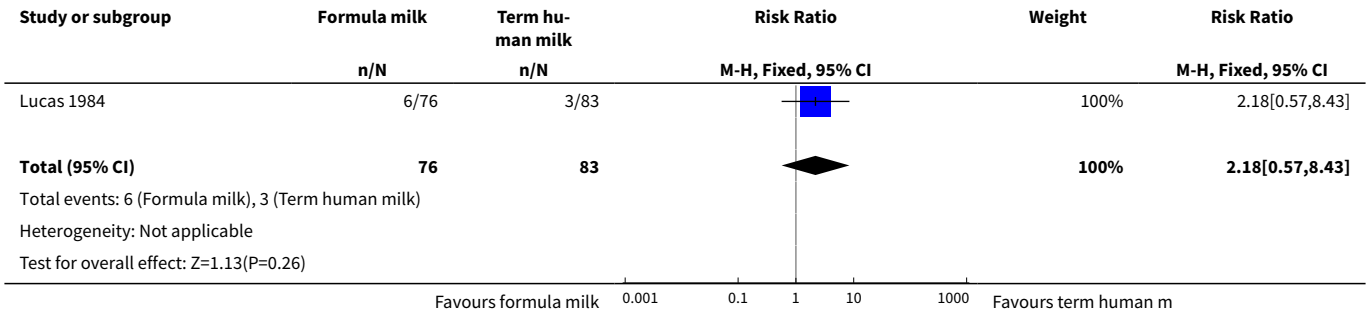
Analysis 5.1. Comparison 5 Calorie-supplemented, protein-enriched formula versus term human milk, Outcome 1 Short term change in crown-heel length (mm/week).



Analysis 5.2. Comparison 5 Calorie-supplemented, protein-enriched formula versus term human milk, Outcome 2 Short term change in head circumference (mm/week).



Analysis 5.3. Comparison 5 Calorie-supplemented, protein-enriched formula versus term human milk, Outcome 3 Necrotising enterocolitis.



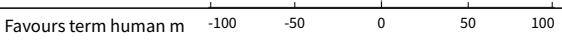
Comparison 6. Calorie-supplemented, protein-enriched and mineral-supplemented formula versus term human milk

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Short term weight change (g/day)	1	76	Mean Difference (IV, Fixed, 95% CI)	14.5 [10.86, 18.14]
2 Short term change in crown-heel length (mm/week)	1	76	Mean Difference (IV, Fixed, 95% CI)	4.0 [1.93, 6.07]
3 Short term change in head circumference (mm/week)	1	76	Mean Difference (IV, Fixed, 95% CI)	4.0 [2.53, 5.47]
4 Necrotising enterocolitis	1	81	Risk Ratio (M-H, Fixed, 95% CI)	4.22 [0.21, 85.27]
5 Brazelton Neonatal Behavioural Assessment Scale (response to auditory and visual stimuli)	1	76	Mean Difference (IV, Fixed, 95% CI)	0.80 [0.26, 1.34]
6 Brazelton Neonatal Behavioural Assessment Scale (response to inanimate objects)	1	76	Mean Difference (IV, Fixed, 95% CI)	2.5 [1.35, 3.65]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7 Short term change in triceps skinfold thickness (mm/week)	1	76	Mean Difference (IV, Fixed, 95% CI)	0.14 [0.01, 0.27]
8 Feed intolerance or diarrhoea	1	81	Risk Ratio (M-H, Fixed, 95% CI)	1.68 [0.16, 17.82]

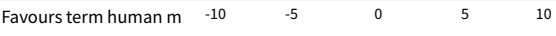
Analysis 6.1. Comparison 6 Calorie-supplemented, protein-enriched and mineral-supplemented formula versus term human milk, Outcome 1 Short term weight change (g/day).

Study or subgroup	Formula milk N	Formula milk Mean(SD)	Term human milk N	Term human milk Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Tyson 1983	42	29.8 (10)	34	15.3 (6)		100%	14.5[10.86,18.14]
Total ***	**42**		**34**			**100%**	**14.5[10.86,18.14]**
Heterogeneity: Not applicable							
Test for overall effect: Z=7.82(P<0.0001)							



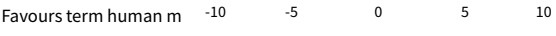
Analysis 6.2. Comparison 6 Calorie-supplemented, protein-enriched and mineral-supplemented formula versus term human milk, Outcome 2 Short term change in crown-heel length (mm/week).

Study or subgroup	Formula milk N	Formula milk Mean(SD)	Term human milk N	Term human milk Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Tyson 1983	42	11 (4)	34	7 (5)		100%	4[1.93,6.07]
Total ***	**42**		**34**			**100%**	**4[1.93,6.07]**
Heterogeneity: Not applicable							
Test for overall effect: Z=3.79(P=0)							

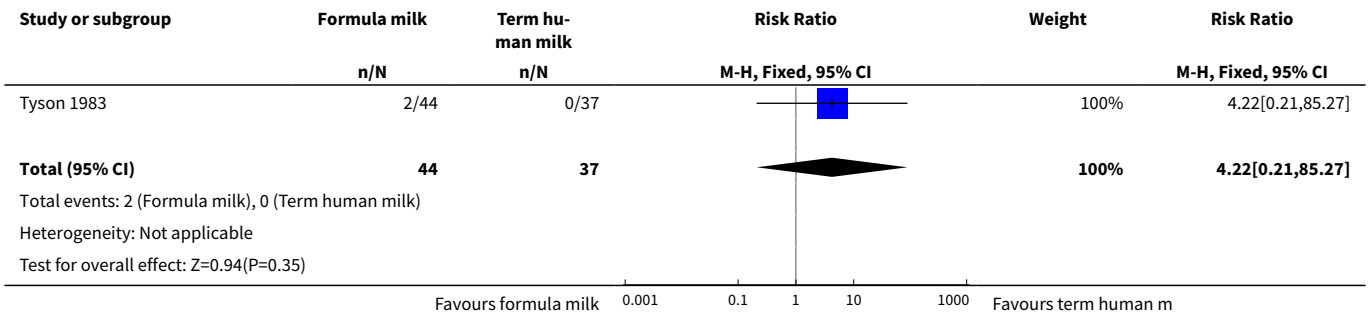


Analysis 6.3. Comparison 6 Calorie-supplemented, protein-enriched and mineral-supplemented formula versus term human milk, Outcome 3 Short term change in head circumference (mm/week).

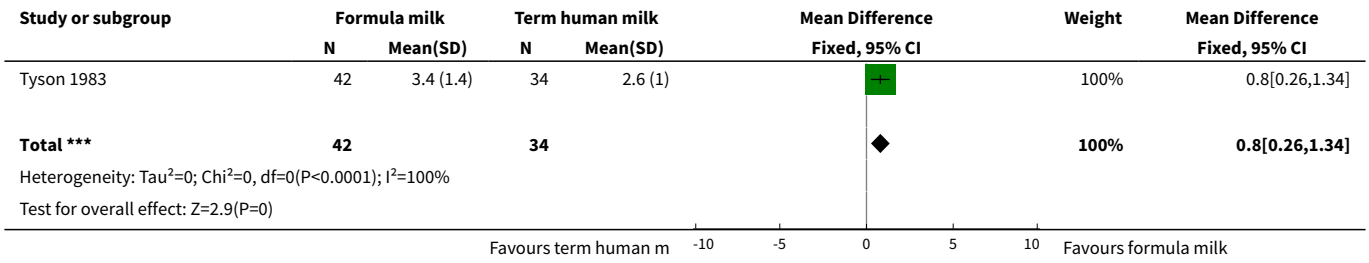
Study or subgroup	Formula milk N	Formula milk Mean(SD)	Term human milk N	Term human milk Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Tyson 1983	42	12 (2)	34	8 (4)		100%	4[2.53,5.47]
Total ***	**42**		**34**			**100%**	**4[2.53,5.47]**
Heterogeneity: Not applicable							
Test for overall effect: Z=5.32(P<0.0001)							



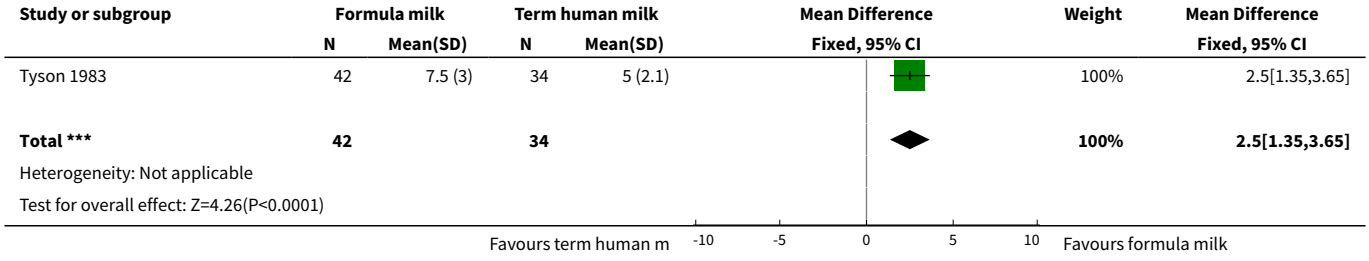
Analysis 6.4. Comparison 6 Calorie-supplemented, protein-enriched and mineral-supplemented formula versus term human milk, Outcome 4 Necrotising enterocolitis.



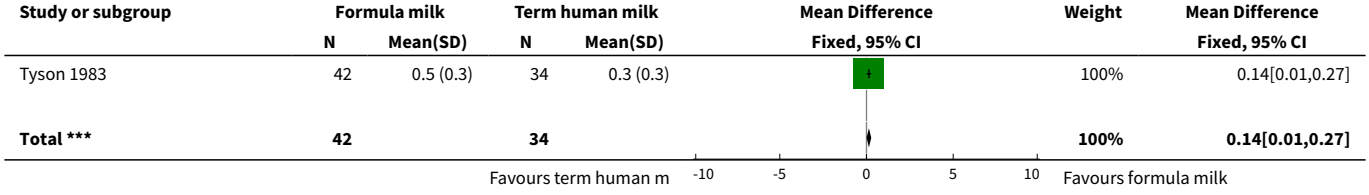
Analysis 6.5. Comparison 6 Calorie-supplemented, protein-enriched and mineral-supplemented formula versus term human milk, Outcome 5 Brazelton Neonatal Behavioural Assessment Scale (response to auditory and visual stimuli).

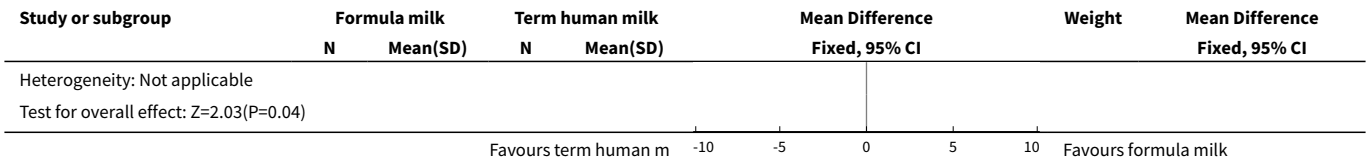


Analysis 6.6. Comparison 6 Calorie-supplemented, protein-enriched and mineral-supplemented formula versus term human milk, Outcome 6 Brazelton Neonatal Behavioural Assessment Scale (response to inanimate objects).

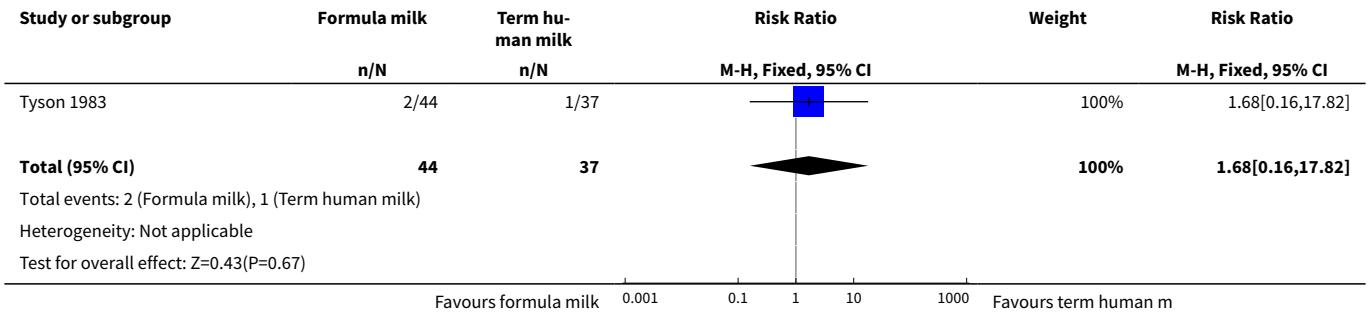


Analysis 6.7. Comparison 6 Calorie-supplemented, protein-enriched and mineral-supplemented formula versus term human milk, Outcome 7 Short term change in triceps skinfold thickness (mm/week).





Analysis 6.8. Comparison 6 Calorie-supplemented, protein-enriched and mineral-supplemented formula versus term human milk, Outcome 8 Feed intolerance or diarrhoea.



WHAT'S NEW

Date	Event	Description
10 May 2017	Amended	Converted to new review format.

HISTORY

Protocol first published: Issue 1, 2001
Review first published: Issue 4, 2001

Date	Event	Description
17 August 2001	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

William McGuire (WM) and Mary Anthony (MYA) developed the protocol and undertook the original review in 2000. Ginny Henderson (GH) updated the review in 2003.

GH and WM screened the title and abstract of all studies identified by the search strategy. MYA and WM screened the full text of the report of each study identified as of potential relevance. MYA and WM extracted the data separately, compared data, and resolved differences by consensus. GH, MTA, and WM completed the final (updated) review.

DECLARATIONS OF INTEREST

None

SOURCES OF SUPPORT

Internal sources

- Tayside Institute of Child Health, Ninewells Hospital and Medical School, Dundee, UK.

External sources

- Systematic Reviews Training Unit, Institute of Child Health, London, UK.
- Royal College of Paediatrics and Child Health, UK.
- Tenovus, Scotland, UK.

INDEX TERMS

Medical Subject Headings (MeSH)

*Infant Formula; *Milk, Human; Child Development; Enteral Nutrition [*methods]; Food, Fortified; Head [growth & development]; Infant Nutritional Physiological Phenomena; Infant, Low Birth Weight [*growth & development]; Infant, Premature [*growth & development]; Randomized Controlled Trials as Topic; Weight Gain

MeSH check words

Humans; Infant, Newborn